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ORIGINAL ARTICLE

Osimertinib in advanced non-small cell lung cancer (NSCLC) harboring different EGFR uncommon variants: real-world data from the Italian biomarker ATLAS database

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Background: Uncommon EGFR mutations (ucEGFR mut) account for 10%-15% of epidermal growth factor receptor (EGFR) oncogenic alterations in non-small cell lung cancer (NSCLC) and display heterogeneous sensitivity to EGFR tyrosine kinase inhibitors.

Materials and methods: Clinical, pathological, and molecular data from patients with advanced NSCLC harboring ucEGFR mut (excluding ex20 insertions) and treated with first-line osimertinib were retrospectively collected from the Italian ATLAS registry.

Results: From January 2019 to January 2025, 212 patients were included. Median age was 69 years (range 24-90); 61.3% were female and 47.6% had a smoking history. Exon 19 deletions/insertions (ex19 delins) were the most frequent ucEGFR mut (55.7%), followed by L816Q (10.8%), G719X (8.5%), and D761N (7.5%). Tumor protein p53 and phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha (PIK3CA) comutations were present in 43.3% and 10.4% of cases. The overall response rate (ORR) was 66% [95% confidence interval (CI) 58-73], median progression-free survival (mPFS) was 18.3 months (95% CI 14.6-19.7), and median overall survival (mOS) was 34.5 months (95% CI 26.1-42.9). Patients with ex19 delins showed superior outcomes versus other ucEGFR mut: ORR (74.3% versus 55%, $P = 0.007$), mPFS (25.3 versus 12.6 months, $P = 0.001$), and mOS (41.7 versus 30.4 months, $P = 0.03$), as well as different resistance mechanisms. Targetable acquired alterations (mesenchymal—epithelial transition amplification and C797S mutations) were detected predominantly in patients with ex19 delins, leading to the use of second-line molecularly matched therapies mainly in this subgroup. Patients with ex19 delins showed similar survival outcomes (25.3 versus 25.4 months, $P = 0.55$) and resistance patterns compared with a cohort of patients harboring the common exon 19 deletion (ELREA) extracted from the ATLAS registry. Among ex19 delins, variants starting at codon 746 achieved longer survival compared with those starting at codon 747.

Conclusions: Osimertinib exhibited meaningful differences in efficacy and resistance mechanisms across distinct ucEGFR mut. Notably, ex19 delins showed comparable survival outcomes and resistance patterns to classical ex19 deletions, albeit with heterogeneous osimertinib sensitivity depending on the deletion—insertion starting codon.

Key words: exon 19 deletions—insertions (ex19 delins), non-small-cell lung cancer, osimertinib, tyrosine kinase inhibitors, uncommon EGFR mutation

INTRODUCTION

With an estimated 2.5 million new cases in 2022, lung cancer is one of the leading causes of cancer-related death worldwide, accounting for up to 20% of all cancer deaths in both sexes.[1] Epidermal growth factor receptor (EGFR) mutations encompass a broad spectrum of gene alterations and are present in up to 15% of Caucasian patients with

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non-small-cell lung cancer (NSCLC) and in ∼50% of Asian patients, with a higher prevalence among young women and never-smokers.[2]

The most frequent EGFR mutations include the exon 19 deletion (ex19del), which spans amino acid residues 746_750 (ELREA), and the L858R substitution in exon 21, together accounting for 70%-85% of activating EGFR mutations.[2] These mutations are defined as 'common mutations' and result in downstream EGFR signaling, driving cellular proliferation and tumorigenesis.[3]

Approximately 10%-15% of EGFR-positive NSCLCs harbor uncommon EGFR (ucEGFR) mutations, which are generally more frequent in smokers and males.[4,5] Among these, G719X, L861Q, and S768I are the most prevalent and are defined as 'major ucEGFR mutations', to distinguish them from other rare mutations, such as exon 18 deletion and exon 20 insertion.[6]

The MD Anderson Cancer Center (MDACC) structure-based classification of ucEGFR mutations reflects their heterogeneous sensitivity to EGFR tyrosine kinase inhibitors (EGFR-TKIs) and distinguishes four classes: classical-like, T790M-like, P-loop/α-helix compressing (PACC), and exon 20 insertions, which form their own subclass.[7] Although classical-like and T790M-like mutations remain more sensitive to third-generation EGFR-TKIs, PACC mutations are more responsive to second-generation EGFR-TKIs.[7] Furthermore, patients harboring more than one EGFR mutation (compound mutations), whether common and/or uncommon, exhibit heterogeneous responses depending on the sensitivity of each mutation to EGFR-TKIs.[7,8] Rarely, ucEGFR mutations may have a germline origin and, in such cases, are generally associated with common EGFR mutations.[9]

Exon 19 deletion—insertion mutations (ex19 delins) represent a novel subset of EGFR mutations, characterized by diverse in-frame deletions and insertions that alter the β3/αC-helix loop structure of the receptor, finally resulting in EGFR signaling activation. The most commonly described ex19 delins include L747_P753delinsS (6%), L747_A750delinsP (3.9%), and E746_S752delinsV (3%), which exhibit heterogeneous EGFR-TKI sensitivity in preclinical studies.[10,11] From a structural perspective, differences in the exact starting codon of ex19 delins may result in variable stabilization of the αC-helix and the ATP-binding pocket, potentially influencing EGFR-TKI sensitivity across distinct ex19 delins variants and resulting in different treatment outcomes between ex19 delins and other ex19 deletions such as the p.746_750 deletion ELREA.[10,11]

Notably, it remains undefined whether ex19 delins should be classified alongside common EGFR ex19 deletions or considered part of ucEGFR mutations, as different studies have categorized them heterogeneously.[12-14]

In the present study, ex19 delins were intentionally classified as ucEGFR mutations to specifically address this ongoing ambiguity and to explore their clinical and biological behavior as a distinct molecular subgroup.

The optimal choice of EGFR-TKIs for treating ucEGFR mutations remains controversial in clinical practice. A pooled analysis of the LUX-Lung 2/3/6 trials demonstrated the promising efficacy of the second-generation EGFR-TKI afatinib in advanced NSCLCs with ucEGFR mutations.[15] Furthermore, a recent randomized trial showed improved responses and median progression-free survival (mPFS) with afatinib compared with platinum-based chemotherapy in patients with NSCLC harboring ucEGFR.[16]

Osimertinib is an irreversible, third-generation EGFR-TKI that has demonstrated improved survival compared with first- and second-generation EGFR-TKIs in advanced NSCLCs harboring common EGFR mutations, along with better intracranial activity and safety profiles.[17]

Nevertheless, despite its superiority in common EGFR mutations, the therapeutic potential of osimertinib in patients with ucEGFR mutations remains unclear. Retrospective studies have reported encouraging efficacy data for osimertinib in advanced NSCLC harboring ucEGFR mutations, with response rates of 50%-60% and mPFS ranging from 8 to 10 months.[18,19]

More recently, the UNICORN trial, a single-arm phase II study, evaluated first-line osimertinib in patients with NSCLC harboring various ucEGFR mutations, not only reporting an overall response rate (ORR) of 55% and a mPFS of 9.4 months but also highlighting heterogeneous outcomes across the different mutation subtypes.[20]

The third-generation, highly selective EGFR-TKI lazertinib has demonstrated efficacy in patients harboring major ucEGFR mutations.[21] Furthermore, in the CHRYSALIS-2 trial, the combination of lazertinib with the bispecific antibody targeting EGFR and mesenchymal—epithelial transition (MET), amivantamab, demonstrated durable antitumor activity, achieving an ORR of 57% and a mPFS of 19.5 months in treatment-naïve NSCLCs harboring ucEGFR mutations.[22]

Available studies suggest that the biological profiles, EGFR-TKI sensitivities, and resistance mechanisms may differ among ucEGFR mutations. Particularly, given the ambiguity of their classification, ex19 delins remain a subject of debate, especially in the absence of large, dedicated studies. Therefore, a better understanding of the biological characteristics and treatment responses within the ucEGFR landscape could facilitate more personalized therapeutic strategies and guide the selection of optimal EGFR-TKIs.

In this context, our study aimed to investigate the efficacy of osimertinib across various ucEGFR mutations, with a particular focus on ex19 delins, by evaluating survival outcomes and key resistance mechanisms within the real-world Italian multicenter ATLAS registry.

MATERIALS AND METHODS

Study design

This multicenter, retrospective real-world study included patients with advanced NSCLC harboring EGFR mutations from the ATLAS Italian registry (biomarkersatlas.com). Eligible patients were adults (≥18 years) with histologically or cytologically confirmed stage IIIB/C or IV NSCLC (AJCC

eighth edition), harboring ucEGFR identified by validated assays in certified local laboratories and treated with first-line osimertinib.

UcEGFR mutations included all pathogenic EGFR mutations except classical/common mutations (L858R and common ex19 deletions) and EGFR ex20 insertions. They were divided into two groups: group 1, comprising ex19 delins, and group 2, including all other ucEGFR mutations (Supplementary Table S1, available at https://doi.org/10.1016/j.esmoop.2026.108369). Furthermore, given the genetic similarity between exon 19 delins (group 1) and exon 19 deletions (ELREA), and the differences in osimertinib efficacy reported between exon 19 deletions (ELREA) and exon 21 L858R mutations,[17] we decided to compare group 1 alterations and exon 19 deletions (ELREA).

All enrolled patients in the ATLAS registry provided informed consent according to Italian requirements. Data were extracted from medical charts and/or electronic health records across 58 Italian centers and archived in an electronic case report form at investigators' sites. The study was conducted in accordance with the International Conference on Harmonization Guidelines on Good Clinical Practice and the Declaration of Helsinki. The ATLAS protocol was approved by the Independent Ethics Committee of the coordinating center at the University of Turin (approval number: 0006981) and subsequently by the local ethics committees of all participating centers.

Study objectives

The primary objective of this study was to characterize the clinicopathological and molecular features of patients with advanced NSCLC harboring ucEGFR mutations and to evaluate first-line osimertinib efficacy. Treatment outcomes included ORR, intracranial ORR (icORR), intracranial PFS (icPFS), mPFS, and median overall survival (mOS). Secondary objectives were to explore mechanisms of resistance to osimertinib, assess the efficacy of subsequent therapies, and compare clinicopathological characteristics and survival outcomes among patients with ex19 delins, other ucEGFR mutations, and classical ex19 deletions (ELREA).

Statistical analyses

Baseline clinical—pathological and molecular characteristics, as well as progression patterns, were summarized using descriptive statistics [means, medians, and absolute or relative frequencies with two-sided 95% confidence intervals (CIs)].

ORR was defined as the proportion of participants achieving complete response (CR) or partial response (PR) according to RECIST v1.1,[23] assessed by local investigators using total-body CT scans carried out every 3 months. Disease-control rate (DCR) was defined as the proportion of participants achieving CR, PR, or stable disease as the best overall response.

icORR was reported for intracranial best response to osimertinib according to Response Assessment in Neuro-Oncology criteria, as assessed by local investigators using brain MRI carried out every 3 months.[24] mPFS was defined as the time from treatment start to disease progression or death, whichever occurred first, and mOS as the time from treatment start to death from any cause. Both mPFS and mOS were estimated using the Kaplan—Meier method.

Medians and two-sided 95% CIs were calculated and Kaplan—Meier plots for mPFS and mOS were generated. The log-rank test ($P < 0.05$) was used for comparisons. Correlations were assessed using chi-square, Mann—Whitney, or two-tailed Fisher's exact tests, and multiple logistic regression. The impact of clinical—pathological features on outcomes was evaluated with the log-rank test and Cox proportional hazards model. Analyses were conducted using IBM SPSS Statistics v25 (IBM Corp, Armonk, NY) and GraphPad Prism v9 (GraphPad Software, San Diego, CA).

RESULTS

Baseline characteristics

Between January 2019 and January 2025, the ATLAS registry recorded 208 NSCLC cases harboring group 1 mutations (9.1% of EGFR-mutated patients) and 280 cases with group 2 alterations (12.2% of EGFR-mutated patients). Among patients with EGFR-positive NSCLC treated for advanced disease, 83.1% ($n = 118$) of those harboring group 1 alterations and 44.1% ($n = 94$) of those with group 2 alterations received first-line osimertinib across 58 Italian centers (Supplementary Figure S1, available at https://doi.org/10.1016/j.esmoop.2026.108369).

Patient and disease characteristics of the study population are summarized in Table 1. Median age at diagnosis was 69 years (range 24-90); the majority of patients were female ($n = 130$, 61.3%), never-smokers ($n = 104$, 49.1%), and had an Eastern Cooperative Oncology Group performance status (ECOG PS) of 0-1 ($n = 179$, 84.4%).

At diagnosis, the majority of NSCLCs presented with stage IV disease ($n = 179$, 84.5%), whereas 30 patients had stage I-III disease (14.1%) and were treated with first-line osimertinib at recurrence. No patients received adjuvant osimertinib after surgery or osimertinib maintenance after chemoradiotherapy for locally advanced disease.

Bone was the most common extrathoracic metastatic site (49.5%), followed by the brain (26.4%). Notably, among 56 patients with brain/central nervous system (CNS) metastases at baseline, 6 (10.7%) received CNS-directed radiotherapy (4 stereotactic radiosurgery and 2 whole-brain radiotherapy) before or concurrent with the initiation of osimertinib.

To determine EGFR status, next-generation sequencing (NGS) was the most common testing method ($n = 166$, 78.3%), followed by RT—PCR ($n = 39$, 18.4%). After molecular profiling, the most frequent ucEGFR mutations were ex19 delins ($n = 118$, 55.7%), followed by L816Q ($n = 23$, 10.8%), G719X ($n = 18$, 8.5%), D761N ($n = 16$, 7.5%), S768I ($n = 3$, 1.4%), and E709K ($n = 3$, 1.4%) (Supplementary Figure S2, available at https://doi.org/10.1016/j.esmoop.2026.108369). The most frequent comutations were

Table 1. Baseline characteristics of patients with NSCLC harboring ucEGFR

Baseline characteristics	*n* (%)
Age, median (min-max)	69 (24-90)
Sex	
Male	82 (38.7)
Female	130 (61.3)
ECOG PS	
0-1	179 (84.4)
≥2	29 (13.7)
Unknown	4 (1.9)
Smoking status	
Active	35 (16.5)
Former	66 (31.1)
Never	104 (49.1)
Unknown	7 (3.3)
Stage at diagnosis	
I-III	30 (14.1)
IV	179 (84.5)
Unknown	3 (1.4)
Histology	
Adenocarcinoma	205 (96.6)
Squamous	6 (2.9)
Other histology	1 (0.5)
Molecular profiling	
NGS	166 (78.3)
RT—PCR	39 (18.4)
Other methods	7 (3.3)
Mutation type	
Ex 19 delins	118 (55.7)
Ex 21 L861Q	23 (10.8)
Ex 18 G719X	18 (8.5)
Ex 19 D716N	16 (7.5)
Ex 20 S768I	3 (1.4)
Ex 18 E709K	3 (1.4)
Compound	19 (9.0)
Others	12 (5.6)
Comutations	
TP53	29 (43.3)
PI3K	7 (10.4)
CTNNB1	3 (5.5)

ECOG PS, Eastern Cooperative Oncology Group performance status; N, number; NGS, next-generation sequencing; TP53, tumor protein p53.

tumor protein p53 (TP53) and PIK3CA, observed in 43.3% and 10.4% of cases, respectively.

Osimertinib efficacy and safety in ucEGFR-mutated NSCLC

At the time of analysis, the median follow-up was 22.1 months (95% CI 15.0-29.3) and efficacy data are presented in Supplementary Table S2 (available at https://doi.org/10.1016/j.esmoop.2026.108369). In the overall population, the ORR was 66% (95% CI 58-73) and the DCR was 91% (95% CI 87-95). With 113 PFS events, the mPFS was 18.3 months (95% CI 15.7-20.9), and the mOS was 34.5 months (95% CI 26.1-42.9) (Supplementary Figure S3, available at https://doi.org/10.1016/j.esmoop.2026.108369). Intracranial activity data were available for 31 of the 56 patients with brain metastases, and the icORR was 67% (95% CI 48-83), with 7 patients (22.8%) achieving an intracranial CR and 14 (45.2%) achieving a PR. The icPFS in the overall population was 17.2 months (95% CI 14.6-19.7). Safety data are consistent with previous findings in the literature and are shown in Supplementary Table S3 (available at https://doi.org/10.1016/j.esmoop.2026.108369).

Comparison between NSCLC with ex19 delins (group 1) and other ucEGFR mutations (group 2)

Among patients treated with first-line osimertinib, when comparing baseline characteristics between NSCLC with group 1 and 2 mutations, we observed a higher incidence of liver metastases (19.1% versus 9.3%, $P < 0.05$) and a more frequent smoking history (53.2% versus 43.2%, $P = 0.06$) in patients with group 2 mutations (Table 2).

Treatment outcomes for group 1 versus group 2 mutations are summarized in Supplementary Table S4 (available at https://doi.org/10.1016/j.esmoop.2026.108369). Patients with group 1 mutations exhibited a higher ORR (74.5% versus 55.0%, $P = 0.007$) and a higher icORR (85.7% versus 52.9%, $P = 0.052$). Notably, a higher proportion of group 2 mutations exhibited primary resistance to osimertinib compared with group 1 ucEGFR mutations (17.5 versus 0.9%, $P < 0.01$), in particular those with ex18 G719X mutations. Specifically, Supplementary Table S5 (available at https://doi.org/10.1016/j.esmoop.2026.108369) provides a summary of efficacy outcomes stratified by each mutation subtype.

Notably, icPFS [39.1 versus 12.7 months, hazard ratio (HR) 2.48, 95% CI 1.07-5.75, $P = 0.034$], mPFS (25.3 versus 12.6 months, HR 2.16; 95% CI 1.49-3.15, $P < 0.01$), and mOS (41.7 versus 30.4 months, HR 1.64, 95% CI 1.05-2.58, $P = 0.03$) were all longer in patients with group 1 compared with those with group 2 mutations (Figure 1 and Supplementary Table S4, available at https://doi.org/10.1016/j.esmoop.2026.108369). The impact of mutation type (groups 1 versus 2) on mPFS and mOS remained consistent across all subgroups of ucEGFR-mutated patients (including those with a positive smoking history and liver metastases at baseline) (Supplementary Figures S4 and S5, available at https://doi.org/10.1016/j.esmoop.2026.108369). Furthermore, multivariate analysis showed that mutation type (groups 1 versus 2) remained significantly associated with mPFS and mOS (Supplementary Figures S6 and S7, available at https://doi.org/10.1016/j.esmoop.2026.108369).

Finally, we differentiated among group 2 variants, classical-like, and PACC ucEGFR mutations according to the MDACC classification. Patients with group 1 alterations showed better survival outcomes compared with patients with either PACC or classical-like alterations (Supplementary Table S6, available at https://doi.org/10.1016/j.esmoop.2026.108369).

Compared with PACC, group 1 showed higher ORR (74.5% versus 56.3%, $P = 0.05$), lower rates of primary resistance (1% versus 18.8%, $P < 0.01$), longer mPFS (25.3 versus 11.9 months, $P = 0.01$), and prolonged mOS (41.7

Table 2. Comparison of baseline characteristics between ex19 delins (group 1 ucEGFR mutations), other ucEGFR mutations (group 2 ucEGFR mutations), and ELREA deletions

Baseline characteristics	Group 1 ucEGFR mut		Group 2 ucEGFR mut		*P* (group 1 versus 2)	ELREA		*P* (group 1 versus ELREA)
	n	%	*n*	%		*n*	%	
Age, median (range)	68 (33-90)		69 (24-86)		0.877	67 (25-90)		0.850
Sex					0.919			0.251
Male	46	39.0	36	38.3		150	33.3	
Female	72	61.0	58	61.7		300	66.7	
ECOG PS					0.966			0.307
0-1	98	83.1	81	86.2		395	87.7	
≥2	16	13.6	13	13.8		47	10.4	
Unknown	4	3.3	0	0		8	1.9	
Smoking history					0.061			0.050
Positive	51	43.2	50	53.2		144	32.0	
Never	66	55.9	38	40.4		280	62.3	
Unknown	1	0.9	6	6.4		26	5.7	
Stage at diagnosis					0.752			0.586
I-III	16	13.5	14	14.8		52	11.6	
IV	101	85.6	78	83.0		388	86.2	
Unknown	1	0.9	2	2.2		10	2.2	
Histology					0.517			0.230
Adenocarcinoma	115	97.4	90	95.7		436	96.9	
Squamous	3	2.6	3	3.2		6	1.3	
Other	0	0	1	1.1		8	1.8	
TP53					0.397			0.820
Mutated	19	47.5	10	37.0		41	44.6	
Wild-type	21	52.5	17	63.0		51	55.4	
Metastatic sites								
Lung	62	52.5	41	43.6	0.196	237	52.7	0.350
Pleural	49	41.5	33	35.1	0.340	188	41.8	0.420
Brain	30	25.4	26	27.7	0.714	131	29.1	0.180
Liver	11	9.3	18	19.1	0.039	72	16.0	0.031
Bone	59	50	46	48.9	0.878	221	49.1	0.469
Nodes	80	67.8	53	56.4	0.088	286	63.6	0.684

ECOG PS, Eastern Cooperative Oncology Group performance status; ex19 delins, exon 19 deletion—insertions; TP53, tumor protein p53; ucEGFR, uncommon EGFR mutation.

versus 28.3 months, $P = 0.04$). Compared with classical-like mutations, group 1 showed higher ORR (74.5% versus 58.3%, $P = 0.07$), lower rates of primary resistance (1% versus 8.3%, $P = 0.02$), longer mPFS (25.3 versus 12.6 months, $P = 0.01$), and longer mOS (41.7 versus 31.3 months, $P = 0.05$).

Comparison between NSCLC with group 1 ucEGFR mutations and common ex19 deletions (ELREA)

Given the superior efficacy of osimertinib in patients with group 1 ucEGFR mutations compared with those harboring group 2 mutations, we evaluated the characteristics and treatment outcomes of the group 1 population with another cohort of 450 patients with advanced NSCLC carrying the common ex19 deletion (ELREA).

When comparing baseline characteristics, NSCLC with group 1 ucEGFR mutations exhibited a higher frequency of smoking history (43.2% versus 32.0%, $P = 0.05$) but a lower incidence of liver metastases (9.3% versus 16.0%, $P = 0.03$) (Table 2).

Interestingly, treatment outcomes were similar between patients with group 1 ucEGFR mutations and those with ex19 deletions: ORR (74.5% versus 80.3%, $P = 0.16$), mPFS (25.3 versus 25.4 months, HR 1.09, 95% CI 0.81-1.46, $P = 0.55$), and mOS (41.7 versus 41.6 months, HR 1.02, 95% CI 0.71-1.16, $P = 0.89$) (Figure 1 and Supplementary Table S4, available at https://doi.org/10.1016/j.esmoop.2026.108369).

Comparison between NSCLC with ucEGFR mutations and common ex19 deletion in Memorial Sloan Kettering CHORD

We analyzed a publicly available, multicohort genomic dataset including 2429 samples from patients with NSCLC harboring pathogenic EGFR mutations, obtained from the cBioPortal for Cancer Genomics, identifying 239 cases with group 1 ucEGFR mutations (9.8% of cases). Cases from the publicly accessible Memorial Sloan Kettering (MSK) cohort were selected as an external validation cohort.

In total, we selected 378 patients treated with first-line osimertinib, including 75, 84, and 219 NSCLCs harboring group 2, group 1 ucEGFR mutations, and common ex19 deletions, respectively.

The available characteristics of this independent cohort from the MSK-CHORD are shown in Supplementary Table S7 (available at https://doi.org/10.1016/j.esmoop.2026.108369). Consistent with our data, the MSK cohort demonstrated worse mOS in patients with group 2 compared with group 1 ucEGFR mutations (38.9 versus 53.7 months, HR 0.52, 95% CI 0.33-0.83, $P = 0.006$) as well similar mOS between NSCLCs with group 1 ucEGFR

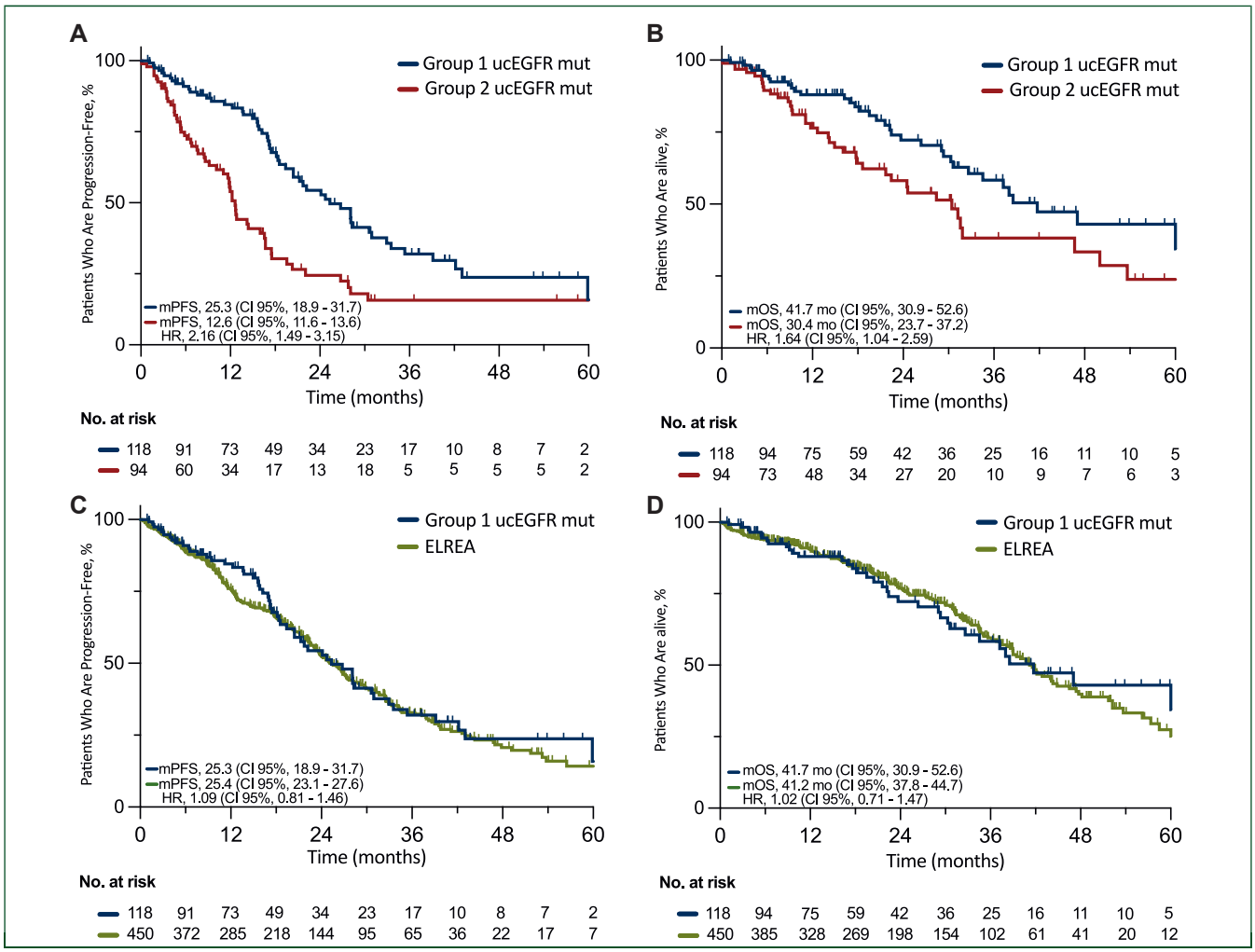

Figure 1. Comparison of osimertinib outcomes between ex19 delins (group 1 ucEGFR mutations), other ucEGFR (group 2 ucEGFR mutations), and common ex19 deletions (ELREA). Kaplan–Meier curves showing mPFS and mOS across mutation subgroups: (A) Progression-free survival (PFS) comparison between ex19 delins and other ucEGFR, (B) Overall survival (OS) comparison between ex19 delins and other ucEGFR, (C) PFS comparison between ex19 delins and common Ex19 deletions (ELREA), and (D) OS comparison between ex19 delins and common Ex19 deletions (ELREA).

CI, confidence interval; ex19 delins, exon 19 deletions–insertions; mOS, median overall survival; mPFS, median progression-free survival; no. at risk, number at risk; ucEGFR, uncommon EGFR mutation.

mutations and those with ex19 deletions (53.7 versus 52.1 months, HR 0.83, 95% CI 0.54-1.26, $P = 0.39$).

Heterogeneous treatment outcomes among NSCLCs harboring group 1 ucEGFR mutations

Considering the molecular heterogeneity among group 1 mutations, we compared the clinical characteristics and treatment outcomes of patients with NSCLC harboring ex19 delins starting at codon 746 to those starting at codon 747 (ex19 delins starting at codon 744 were excluded from this analysis due to the limited sample size of this subgroup).

Clinical characteristics were similar between the two populations; however, NSCLC with ex19 delins starting at codon 746 exhibited a higher frequency of metastasis at diagnosis (93.9% versus 80.9%, $P = 0.02$) and the presence of liver metastases (16.3% versus 4.4%, $P = 0.03$) (Supplementary Table S8, available at https://doi.org/10.1016/j.esmoop.2026.108369).

Patients with ex19 delins starting at codon 746 showed better mPFS (42.1 versus 21.7, HR 2.29, 95% CI 1.27-4.12, $P = 0.004$), and mOS (60.0 versus 32.6, HR 3.13, 95% CI 1.64-5.96, $P < 0.01$) (Figure 2 and Supplementary Tables S9 and S10, available at https://doi.org/10.1016/j.esmoop.2026.108369).

Although ex19 delins starting at codon 746 were associated with adverse prognostic characteristics, they were also associated with improved survival outcomes. However, due to the limited number of patients with liver metastases ($n = 11$) or localized-stage disease at diagnosis ($n = 15$), a separate analysis of treatment outcomes according to the starting codon (746 versus 747) within these subgroups. Notably, in the multivariable analysis, ex19 delins starting at codon 746 remained independently associated with longer mPFS and mOS compared with ex19 delins starting at codon 747 (Supplementary Figures S8 and S9, available at https://doi.org/10.1016/j.esmoop.2026.108369).

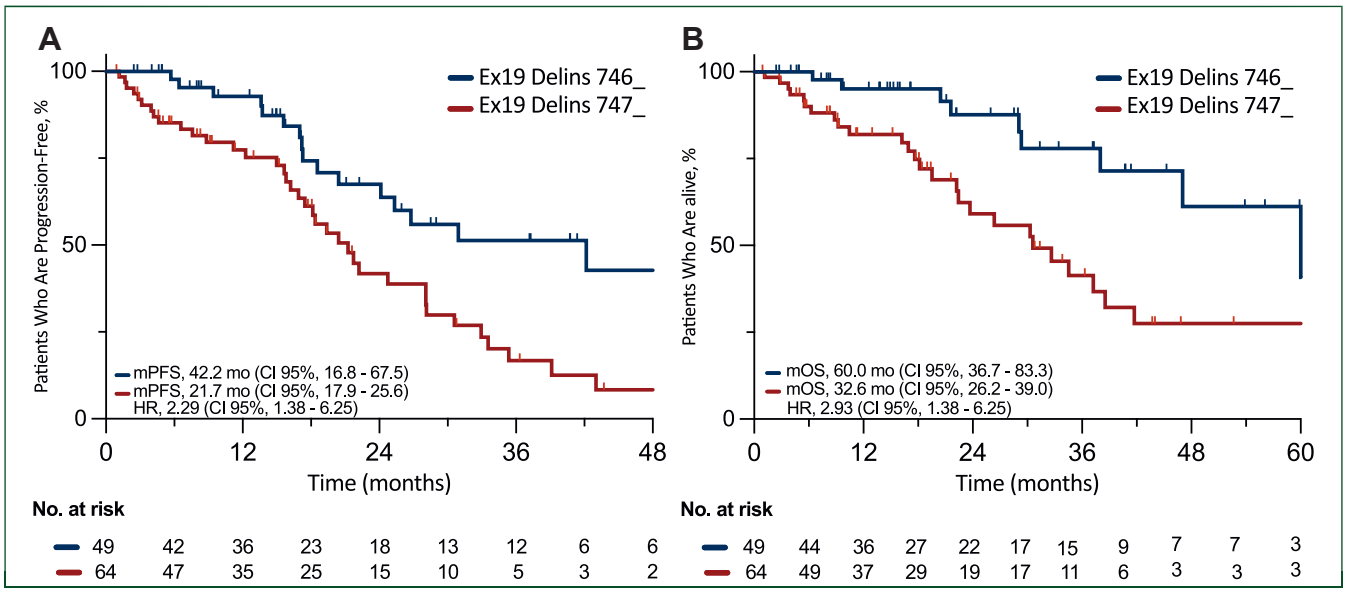

Figure 2. Comparison of osimertinib outcomes between codon 746_ and ex19 delins starting at codon 747_. Kaplan–Meier curves showing mPFS and mOS across mutation subgroups: (A) Progression-free survival comparison between codon 746_ and ex19 delins starting at codon 747_ and (B) Overall survival comparison between codon 746_ and ex19 delins starting at codon 747_.

CI, confidence interval; ex19 delins, exon 19 deletions–insertions; mOS, median overall survival; mPFS, median progression-free survival; no. at risk, number at risk.

Patterns of disease progression and molecular reassessment after disease progression

At the time of data analysis, 98 patients (43.3%) with NSCLC harboring ucEGFR mutations had progressed on first-line osimertinib. The most common sites of disease progression were the lung (32.7%), followed by the brain (21.4%) and the bone (18.4%). Interestingly, higher rates of brain (27.5% versus 12.8%, $P = 0.07$), liver (13.7% versus 4.3%, $P = 0.10$), and bone (25.5% versus 10.6%, $P = 0.06$) progression were observed in patients with group 2 mutations than in those with group 1 mutations.

Among patients with ucEGFR mutations (groups 1 and 2), 37 patients (34.7%) underwent tissue rebiopsy and 14 (13.1%) underwent liquid biopsy, including 3 patients who underwent both analyses. Among patients harboring the exon 19 deletion (ELREA), tissue rebiopsy, liquid biopsy, and both analyses were carried out in 62 (31.3%), 11 (5.5%), and 20 (10.1%) patients, respectively (Figure 3).

Molecular profiling at tumor progression identified the presence of acquired resistance mechanisms in 14 cases (31.1%). Specifically, MET amplification was detected in six cases (13.3%), acquisition of the C797S mutation in six cases (13.3%), neuroendocrine transformation in two cases (4.4%), and acquisition of a BRAF mutation in two cases (4.4%). Acquired resistance mechanisms were more frequently detected in patients with group 1 ucEGFR mutations than in those with group 2 ucEGFR mutations (42.8% versus 17.6%), with distinct patterns of gene alterations observed between the two groups (Supplementary Table S11 and Figure S10, available at https://doi.org/10.1016/j.esmoop.2026.108369).

In contrast, when comparing group 1 ucEGFR mutations with ex19 deletions (ELREA), the incidence of acquired resistance mechanisms (42.8% versus 35.4%) and the distribution of gene alterations were similar between the two molecular groups. Analogously, a similar but not clear difference in resistance pattern was noted between ex19 delins starting at codon 746 and 747 (Figure 3).

Subsequent treatment lines

Among the 98 patients who experienced disease progression, 42 (42.8%) received second-line systemic therapy (Supplementary Table S12, available at https://doi.org/10.1016/j.esmoop.2026.108369), most commonly platinum-based chemotherapy (54.8% of cases).

The ORR was 38% (95% CI 21-55), the mPFS was 7.4 months (95% CI 5.4-9.3), and the mOS was 10.5 months (95% CI 2.8-18.1). Patients harboring group 1 alterations showed similar ORR (37.2% versus 40.0%) but an increased mPFS (8.9 versus 5.1, HR 2.55, 95% CI 1.08-6.02, $P = 0.03$) compared with patients harboring group 2 alterations.

After tumor rebiopsy, nine patients (seven with group 1 and two with group 2 ucEGFR mutations) received molecularly matched treatment, including four NSCLCs acquiring MET amplification treated with anti-MET TKIs and three NSCLCs acquiring the C797S mutation treated with gefitinib. Patients treated with molecularly matched therapies showed an ORR of 50% (95% CI 15-84), a mPFS of 8.6 months (95% CI 6.1-10.5), and a mOS of 10.3 months (95% CI 7.7-12.8).

DISCUSSION

Although several studies have shown the efficacy of the third-generation EGFR-TKI osimertinib in ucEGFR mutations,[18-20,25] most of them were single-arm and included limited patient numbers, precluding robust assessment of

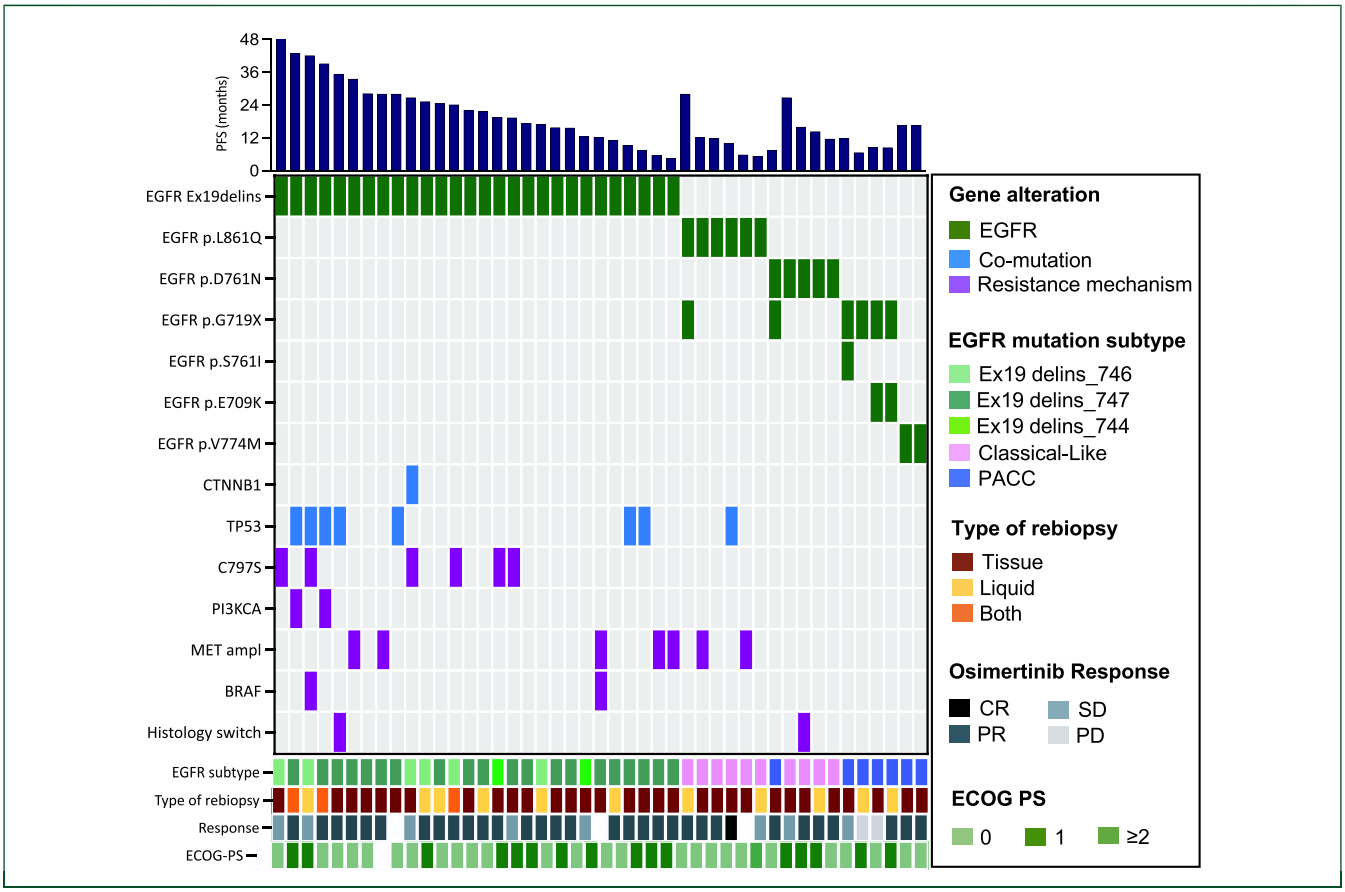

Figure 3. Mechanisms of resistance identified after disease progression on osimertinib in patients with ex19 delins (group 1 ucEGFR mutations) and other ucEGFR (group 2 ucEGFR mutations). This oncoplot illustrates the spectrum of molecular alterations detected at progression. EGFR mutations are shown in green, whereas resistance-associated mutations are shown in purple. The blue bars at the top represent the mPFS for each case. The lower panel displays the type of rebiopsy carried out at progression (tissue biopsy, liquid biopsy, or both), the best response to osimertinib according to RECIST 1.1 (CR, PR, SD, and PD), ECOG PS, and programmed death-ligand 1 tumor proportion score (<1%, 1%-49%, and >50%).

CR, complete response; ECOG PS, Eastern Cooperative Oncology Group performance status; EGFR, epidermal growth factor receptor; ex19 delins, exon 19 deletions—insertions; mPFS, median progression-free survival; PD, progressive disease; PFS, progression-free survival; PR, partial response; SD, stable disease; ucEGFR, uncommon EGFR mutation.

variant-specific efficacy and providing limited insight into resistance mechanisms.[19]

This prompts real-world studies that evaluate effectiveness in routine practice, accrue larger numbers of patients, and allow detailed analysis of resistance mechanisms, ultimately guiding individualized second-line therapies.[26]

This represents a large real-world study that not only confirms the efficacy of osimertinib in NSCLCs harboring ucEGFR mutations but also highlights substantial heterogeneity in both clinical outcomes and resistance mechanisms associated with different ucEGFR mutation variants.

In this study, we divided the study population into two main subgroups: the first comprising ex19 delins, and the second comprising all other ucEGFR mutations (ex20 insertions excluded) in order to better characterize their clinical and molecular features within EGFR-mutated NSCLC.

In the ATLAS registry, the incidence of ex19 delins was similar to that observed in the independent MSK-CHORD cohort, representing ∼9%-10% of overall EGFR alterations and 50%-55% of ucEGFR mutations.[27]

Compared with our findings, previous reports have shown a variable and generally lower incidence of ex19 delins among ucEGFR mutations.[6,13,20] However, the heterogeneous classification of ex 19delins across studies may have led to an underestimation of its prevalence within the ucEGFR-mutated population. In addition, ex19 delins may have been overrepresented among patients receiving first-line osimertinib, potentially reflecting the preferential use of osimertinib in this subgroup, whereas other ucEGFR alterations (i.e. PACC mutations) may have been more frequently treated with alternative TKIs (i.e. afatinib).

Among 212 patients with advanced ucEGFR-mutant NSCLC treated with first-line osimertinib, those harboring ex19 delins showed higher response rates, improved intracranial activity, longer survival, and distinct acquired resistance patterns compared with other ucEGFR mutations.

The favorable outcomes and relatively high prevalence of exon 19 delins have likely influenced the results observed in the overall ucEGFR-mutated population and should therefore be interpreted with caution. This heterogeneity in

osimertinib efficacy further supports the clinical utility of a structure-based classification of EGFR alterations in patients with ucEGFR-mutated NSCLC.[7]

As expected, efficacy across ucEGFR mutations largely reflected the MDACC classification, with better outcomes in classical-like mutations (e.g. D716N) and poorer outcomes in exon 18 G719X mutations, which showed 40% primary resistance.[6] Notably, tumors harboring ex19 delins demonstrated improved survival not only compared with PACC mutations but also compared with other classical-like EGFR alterations.

Our findings corroborate the reduced efficacy of osimertinib in the PACC subgroup, particularly among patients with G719X mutations, supporting the use of afatinib[7] or a combination of lazertinib plus amivantamab in this subgroup.[22] Indeed, PACC mutations alter the orientation of the P-loop and destabilize osimertinib binding. Conversely, afatinib does not interact with the EGFR P-loop and, despite PACC mutations, maintains interactions within the hydrophobic cleft, demonstrating higher efficacy in this molecular subgroup.[7,15] Preclinical studies suggest synergism between EGFR-TKIs and amivantamab in ucEGFR-mutated NSCLC models,[28] and two recent single-arm phase II studies of upfront combination of lazertinib alone or in combination with amivantamab showed promising results in the PACC subgroup.[21,22]

In accordance with European Association of Neuro-Oncology—European Society for Medical Oncology guidelines, only a minority of patients with NSCLC with brain metastases in our real-world cohort received CNS-directed radiotherapy at the time of osimertinib initiation.[29] However, a recent meta-analysis reported improved icPFS with the combination of osimertinib and upfront brain radiotherapy.[30] In addition, the reduced intracranial disease control observed in patients with ucEGFR mutations in our cohort suggests that the optimal integration of brain radiotherapy in this subgroup remains to be defined and deserves further prospective evaluation. Similar to ucEGFR mutations, common EGFR mutations demonstrate heterogeneous sensitivity to osimertinib, with ex19 deletions being associated with superior clinical outcomes compared with the exon 21 L858R mutation.[17] Given the favorable outcomes of ex19 delins among ucEGFR mutations and their molecular characteristics, we compared this subgroup with 450 patients harboring ex19 deletions (ELREA) from the ATLAS registry, observing comparable survival outcomes and resistance mechanisms. These findings were confirmed in an independent cohort from the MSK-CHORD study.[27]

NGS has enabled a more precise characterization of EGFR alterations, allowing differentiation between classic 746_750 deletions (ELREA) and uncommon deletions or deletion—insertions.[31-33] Although ex19 delins remain relatively rare, their detection is expected to increase with broader NGS adoption in clinical practice.

The efficacy of osimertinib in NSCLCs with ex19 delins has been poorly defined, due to uncertainty in classifying these alterations as common or uncommon EGFR mutations and limitations of pre-NGS methods (e.g. RT—PCR), which could not reliably distinguish ex19 delins from other ex19 deletions.[34] Consequently, patients with ex19 delins were likely included in clinical trials of TKI-sensitive EGFR mutations without subgroup-specific outcome reporting.[17,35-38] Furthermore, prior studies exploring the efficacy of osimertinib in patients with ex19 delins have included limited patient numbers and yielded heterogeneous results.[6,12,39]

Our study demonstrated comparable survival outcomes and resistance mechanisms between exon 19 deletions (ELREA) and ex19 delins variants, supporting their classification as 'classical' EGFR alterations. However, substantial heterogeneity in osimertinib efficacy has been observed within the ex19 delins subgroup, emphasizing that ex19 delins should not be considered biologically uniform, as clinically relevant differences emerge according to the deletion—insertion starting codon.

Although exon 19 delins variants starting at codon 746 were associated with higher rates of liver metastases and metastatic disease at diagnosis, subtype analysis showed that variants starting at codon 746 had better survival outcomes than those starting at codon 747. Previous studies suggested poorer outcomes for patients with ex19 delins starting at codon 747 (p.L747_A750delinsP)[39]; however, our data indicate this applies to other ex19 delins variants as well.

A previous biochemical and structural classification indicates that the $\beta 3/\alpha C$ deletion length influences TKI sensitivity. Exon 19 deletions can be grouped into profile 1 ($\leq$3 residues deleted, 8%) and profile 2 ($\geq$4 residues deleted, 92%), with profile 1 exhibiting stronger ATP-binding affinity, reduced osimertinib efficacy, and greater sensitivity to afatinib.[10] The L747_A750delinsP variant belongs to profile 1 and was associated with the worst prognosis, whereas the remaining exon 19 deletions starting at codon 747 were classified as profile 2. Even within profile 2, codon 747-starting variants (L747_T751delinsP, L747_P753delinsQ/S) had worse outcomes than codon 746-starting variants (E746_T751delinsA/P/VA, E746_S752delinsV/A). Notably, patients harboring E746_S752delinsV showed high osimertinib efficacy,[39] despite preclinical data suggesting reduced sensitivity.[11]

The markedly different survival outcomes within the exon 19 deletion subgroup may have direct implications for treatment selection, supporting consideration of alternative TKIs or first-line combination therapies, particularly for high-risk variants.

Recent studies demonstrated that upfront intensification combining EGFR-TKIs with either chemotherapy or amivantamab leads to improved survival outcomes, along with increased toxicity.[35,36] Furthermore, intensification of first-line treatment led to greater benefit in patients with high-risk features (e.g. TP53 comutations or presence of liver metastases).[40]

Recognizing the heterogeneous sensitivity to osimertinib across ex19 delins may help refine the selection of treatment intensification strategies, thereby avoiding

overtreatment in variants with more favorable response profiles. Furthermore, these findings prompt a mutation-specific approach to clinical decision-making and support treatment intensification strategies, particularly for NSCLCs harboring codon 747-starting ex19 delins.

Molecular assessment at disease progression allows for the identification of resistance mechanisms and may guide biomarker-matched therapies.[26]

In our study, molecular analysis revealed distinct patterns of osimertinib resistance in ex19 delins compared with other ucEGFR. Similarly to ex19 deletions (ELREA), ex19 delins more frequently acquired targetable molecular alterations, such as MET amplification, EGFR C797S mutation, and BRAF/KRAS alterations.

These differences in resistance mechanisms may have important implications for guiding subsequent personalized treatment approaches.[41-44] In our study, patients treated in the second line have achieved promising clinical benefits with biomarker-matched therapies. Interestingly, two NSCLC cases harboring the classical-like L861Q mutation acquired MET amplification and were treated with a combination of anti-EGFR and anti-MET TKIs, achieving durable disease control, thereby supporting a tailored therapeutic approach for this mutation subgroup. Conversely, no targetable resistance mechanisms were identified in patients with PACC mutations.

Our study has several limitations. Firstly, its retrospective design and the relatively limited sample size may restrict the generalizability of our findings; however, it is important to note that this is the largest multicenter study published to date evaluating ucEGFR mutations treated with first-line osimertinib. Furthermore, validation of our data in an external, independent cohort from the MSK-CHORD study strongly supports our findings.[27] Despite this, in the case of ultrarare alterations (i.e. ex19 I744_T751delinsVKIPA), the limited number of cases does not allow a specific and strong characterization of each molecular mutation.

Secondly, some degree of heterogeneity was present both in the molecular testing methodologies employed and in the clinical characteristics of the study population. Nevertheless, all analyses were carried out in certified, high-expertise centers, and such heterogeneity reflects the real-world setting in which the study was conducted.

Conclusion

Our study confirms the efficacy of osimertinib in patients with ucEGFR mutations while revealing significant heterogeneity in clinical characteristics, treatment outcomes, and resistance mechanisms across mutation variants. Ex19 delins, although sharing several features with classical ex19 deletions, exhibit substantial internal differences and should not be considered a single therapeutic entity. As intensified first-line combination therapies and biomarker-matched approaches at disease progression have become the standard of care for advanced EGFR-mutated NSCLC, in the era of precision medicine, integrating this heterogeneity into treatment decisions is essential to optimize therapy, improve patient outcomes, and inform future clinical research.

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