ORIGINAL ARTICLE

First-line Osimertinib for Lung Cancer With Uncommon EGFR Exon 19 Mutations and EGFR Compound Mutations

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ABSTRACT

Introduction: Up to 20% of EGFR-mutated NSCLC cases harbor uncommon *EGFR* mutations, including atypical exon 19 and compound mutations. Relatively little is known about the efficacy of osimertinib in these cases.

Methods: Patients treated with first-line osimertinib for NSCLC with rare EGFR exon 19 (non E746_A750del) or compound mutations were included. Response assessment and time to progression were determined using Response Evaluation Criteria in Solid Tumors version 1.1 criteria. Kaplan-Meier analyses were used to estimate progression-free survival (PFS), time to treatment discontinuation (TTD), and overall survival (OS).

Results: Thirty-seven patients with NSCLC harboring an atypical EGFR exon 19 mutation or compound mutation were treated with first-line osimertinib at Johns Hopkins from 2016 to 2021. Overall response rate (ORR) was 76% and median PFS, TTD, and OS were 13 months (95% confidence interval [CI]: 10–15), 22 months (95% CI: 17–32) and 36 months (95% CI, 29–48), respectively. Among atypical exon 19 mutations (n = 25), ORR was 80%, median PFS was 12 months (95% CI: 10–15), median TTD was 19 months (95% CI: 17–38), and median OS was 48 months (95% CI: 25–not reached). Compound mutations (n = 12) had an ORR of 67%, median PFS of 14 months (95% CI: 5–22), median TTD of 26 months (95% CI: 5–36), and median OS of 36 months (95% CI: 20–46). Twelve patients (32%) continued first-line osimertinib after local therapy for oligoprogression.

Conclusions: Osimertinib exhibited favorable outcomes for rare EGFR exon 19 and compound mutations. The heterogeneity in outcomes among these groups of tumors with similar mutations underscores the need for continued reporting and further study of outcomes among rare variants to optimize management for each patient.

Keywords: NSCLC; Osimertinib; Atypical EGFR; EGFR exon 19; Compound EGFR

Introduction

Driver mutations in the *EGFR* gene are found in up to 20% of the cases of NSCLC, with higher prevalence among Asian patients, patients with non-smoking status, female patients, and patients with adenocarcinoma.[1,2] These mutations predominantly span exons 18 to 21 of the EGFR tyrosine kinase domain leading to constitutive activation and dysregulation that result in neoplastic growth.[3] More than 80% of EGFR mutations consist of short in-frame exon 19 deletions or L858R point mutations in exon 21, together referred to as common, or

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classical, mutations. Tumors with these mutations found sensitivity to EGFR tyrosine kinase inhibitors (TKIs).[4] Osimertinib is a third-generation EGFR TKI that selectively inhibits both classical TKI-sensitizing mutations and EGFR T790M resistance mutations.[5,6] Compared with first-generation EGFR TKIs (e.g., gefitinib and erlotinib), osimertinib is associated with significantly longer progression-free survival (PFS; 18.9 mo versus 10.2 mo) and overall survival (OS) (38.6 mo versus 31.8 mo) and is recommended as the standard first-line treatment for patients with NSCLC harboring common EGFR mutations.[5–7]

For the remaining heterogeneous group of uncommon EGFR mutations, responses to EGFR TKIs are variable. The high degree of genotypic diversity and relatively low frequency of each individual uncommon mutation has made them challenging to study. Currently, afatinib is approved for treatment of tumors with EGFR S768I, L861Q, and G719X mutations based on pooled analysis of the LUX-LUNG 2, LUX-LUNG 3, and LUX-LUNG 6 trials, which found an overall response rate (ORR) of 71% and PFS of 10.7 months in this patient population.[8–11] In addition, the bispecific EGFR-MET antibody amivantamab is approved for the treatment of tumors harboring TKI-resistant EGFR exon 20 insertion mutations.[12–14] Otherwise, there is limited clinical data to guide management of uncommon EGFR mutations.

Among EGFR exon 19 mutations, the in-frame deletion E746_A750del accounts for 75% of exon 19 variants, yet over 100 other exon 19 mutations have been identified in NSCLC.[15] Though many atypical exon 19 in-frame deletions and deletion-insertion alterations are grouped in the classification of 'exon 19 deletions' and thus were likely included in clinical trials for NSCLC with TKI-sensitive EGFR mutations, the activity of osimertinib and outcomes for these unique cases are much less clear.[16] Variant-specific structural changes in the EGFR kinase domain confer differences in both intrinsic activation of the mutant EGFR protein and kinetics of TKI activity, thus differentially impacting both natural history and treatment outcomes across specific exon 19 mutation variants[17,18] Multiple retrospective cohorts have investigated clinical outcomes across exon 19 variants treated with first-line first and second generation TKIs,[19–22] but data on outcomes with first-line osimertinib are lacking.

EGFR compound mutations are another group of atypical mutations in which the efficacy of first-line osimertinib remains relatively unknown. An EGFR compound mutation consists of two or more activating mutations in the EGFR tyrosine kinase domain. Although compound mutations often include one TKI-sensitive mutation, the impact of an additional uncommon mutation or TKI-resistant mutation on osimertinib response is unclear.[23]

The ambiguity in clinical decision making for patients with NSCLC harboring uncommon EGFR mutations, including the lack of data on osimertinib in distinct rare exon 19 or compound mutations, indicates a need for further investigation in this space. In this single-institution retrospective study, we characterize the efficacy of first-line osimertinib for uncommon EGFR exon 19 mutations and compound mutations.

Methods

Patients with advanced EGFR-mutated NSCLC, who were initiated on first-line osimertinib at Johns Hopkins Health System between 2016 and 2021, were retrospectively identified using prescription records. Demographic and clinical data were obtained from the electronic medical record. This study was approved by the Institutional Review Board of Johns Hopkins Health System.

Patients were included in the study cohort if diagnostic molecular sequencing analysis confirmed an EGFR exon 19 mutation other than E746_A750del, or an EGFR compound mutation. Compound mutations with at least two distinct pathogenic EGFR mutations were included if at least one was an uncommon EGFR mutation (i.e., other than ex19del, L858R, or T790M). Select de novo co-mutations detected at the time of diagnosis were also recorded. Mechanisms of resistance were analyzed by evaluating acquired mutations in patients who underwent testing after progression on osimertinib by means of tissue biopsy or cell-free DNA liquid assay, or histologic transformation, which was diagnosed on tissue biopsy.

ORR describes the percentage of patients who had a partial or complete response on first-line osimertinib as defined by the Response Evaluation Criteria in Solid Tumors version 1.1.[24] Real-world PFS was measured from the date of first-line osimertinib initiation to the date of radiographic progression as determined by Response Evaluation Criteria in Solid Tumors version 1.1 or the date of death from any cause, whichever occurred first. OS was measured from the date of first-line osimertinib initiation to the date of death from any cause. To account for real-world variations in time points for response assessment (and patients receiving osimertinib post-progression, often with use of local therapy, including radiation), we also describe time to treatment discontinuation (TTD). TTD was measured from the date of first-line osimertinib initiation to the date of osimertinib discontinuation, addition of a new systemic therapy (e.g., chemotherapy with continued osimertinib was considered a second line of treatment), or death from any cause. Patients were censored at the date of previous follow-up. The Kaplan-Meier method was used

to estimate PFS, TTD, and OS. Subgroups were analyzed using Z-tests and log rank tests of equality. Central nervous system (CNS) response rate for patients with untreated brain metastasis at time of osimertinib start and imaging, available for response assessment, was calculated using the RANO-BM criteria.[25] Statistical analysis was completed using STATA version 18.0 (College Station, TX).

Results

Cohort Characteristics

In this single-institution retrospective study, atypical EGFR exon 19 or EGFR compound mutations were identified in 37 of 132 patients (28%) who were initiated on first-line osimertinib at Johns Hopkins between 2016 to 2021. Patient characteristics are detailed in Table 1. The median age at treatment start was 65 (range 33–90). Among the cohort, 24 patients (65%) were female, and 25 (68%) had no history of tobacco smoking. Among current and former smokers, the median number of pack-years reported was 18 (range: 2.5–30). The majority of patients (89%) had advanced disease at initial presentation, while the remaining four patients had received prior definitive therapy for stage I–III NSCLC and later initiated osimertinib as first-line therapy in the metastatic setting. The most common metastatic sites at diagnosis included brain (57%), bone (51%), and pleura or contralateral lung (49%).

Twenty-five patients had NSCLC with a single atypical exon 19 mutation while 12 harbored compound mutations (Fig. 1). While most of the unique uncommon EGFR driver genotypes were represented in a single patient's tumor each, six were represented in two or more cases including E746_S752delinsV (6 patients), L747_T751del (4 patients), and L747_A750delinsP (3 patients). Figure 1 details all EGFR mutations included in this study.

Co-occurring mutations in *TP53* were identified in 16 of 31 tumors (52%) in which *TP53* sequencing was available (Fig. 2). Recurrent baseline co-mutations were noted in three or more tumors in genes *APC, CREBBP, HDAC4, KMT2D,* and *SYNE1*. One tumor with an uncommon exon 19 mutation (E746_E479del) harbored a de novo T790M co-mutation.

Response and Survival Outcomes

For the overall cohort of 37 patients, the ORR on first-line osimertinib was 76%, with a partial response observed in 28 patients (Fig. 2). Three patients (8%) experienced progressive disease as best response. Median follow-up was 38 months. At the end of data collection, 15 patients (41%) were alive, nine patients (24%) remained on first-line osimertinib, and five patients (14%) remained progression-free.

The median PFS observed in this cohort was 13 months (95% confidence interval [CI]: 10–15), and 19

Table 1. Baseline Patient and Tumor Characteristics

Characteristic	Exon 19 Mutations (n = 25)	Compound Mutations (n = 12)	Overall (n = 37)
Age at Treatment Start, Median (range)	62 (32-90)	66 (44-89)	64 (32-90)
Sex, n (%)			
Female	16 (64)	8 (67)	24 (65)
Race, n (%)			
White	13 (52)	7 (58)	20 (54)
Black	7 (28)	0 (0)	7 (19)
Asian	3 (12)	4 (33)	7 (19)
Not reported	2 (8)	1 (8)	3 (8)
Ethnicity, n (%)			
Hispanic or Latino	2 (8)	0 (0)	2 (5)
Non-Hispanic or Latino	23 (92)	12 (100)	35 (95)
ECOG Performance Status			
0-1	22 (88)	11 (92)	33 (89)
2-3	3 (12)	1 (8)	4 (11)
Histology, n (%)			
Adenocarcinoma	24 (96)	12 (100)	36 (97)
Squamous cell carcinoma	1 (4)	0 (0)	1 (3)
Smoking History, n (%)			
Current or former	6 (24)	6 (50)	12 (32)
Never	19 (76)	6 (50)	25 (68)
Prior therapy for locoregional disease	2 (8)	2 (17)	4 (11)
Brain metastases at osimertinib start	15 (60)	6 (50)	21 (57)

ECOG, Eastern Cooperative Oncology Group.

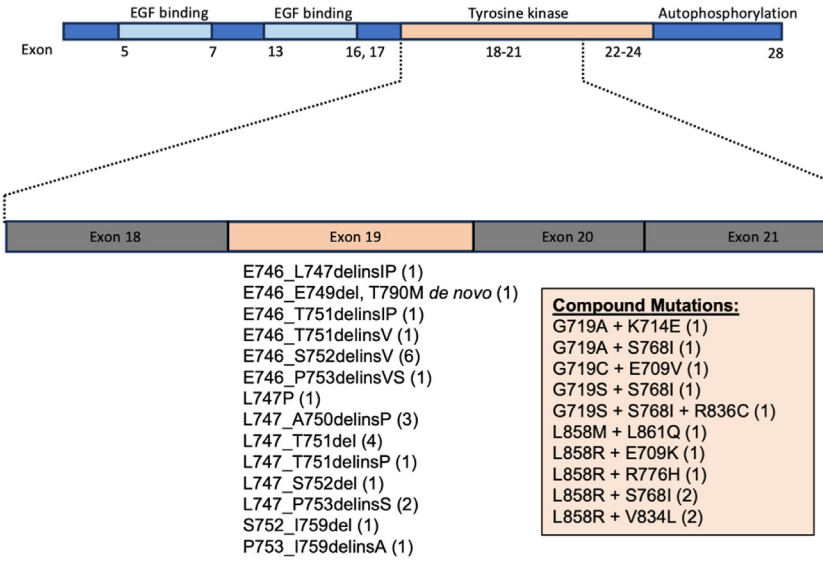


Figure 1. Uncommon EGFR mutations included in study cohort. Single exon 19 mutations are presented in the gene model to the left and compound mutations are described in the box to the right. The number in parentheses denotes the number of cases with each mutation.

patients (51%) remained progression-free at one year on first-line osimertinib (Fig. 3*A*). The most common sites of progression on osimertinib included the lung (54%), lymph nodes (27%), and brain (19%). The median TTD of first-line osimertinib was 22 months (95% CI: 17–32; Fig. 3*B*). Median OS was 36 months (95% CI: 29–48; Fig. 3*C*). Notably, 12 patients (32%) remained on first-line osimertinib past progression with the addition of local therapy for oligoprogressive disease. Among these, the duration of treatment with continued osimertinib ranged from 7 to 37 months. In 11 of these patients, radiotherapy was utilized; and one patient received cryoablation to a site of progression. An osimertinib dose increase from 80 mg to 160 mg was utilized in three patients after leptomeningeal disease progression; duration of treatment with this increased dose ranged from three to 25 months (Fig. 2). Supplementary Table 1 details best overall response, PFS, TTD, and OS for each patient.

Among the subgroup of NSCLC with uncommon EGFR exon 19 mutations (n = 25) the observed ORR was 80%. PFS in different variants ranged from 2 months to ongoing at 54 months, with a median PFS of 12 months (95% CI: 10–15). Median TTD was 19 months (95% CI: 17–38), and median OS was 48 months (95% CI: 25–not reached). Interestingly, classification of the exon 19 deletions and deletion-insertions included in this cohort into the two predominant groups of mutations beginning at E746 (n = 11) or those beginning with L747 (n = 11) found that while the two groups had a similar ORR on osimertinib (82% versus 73% respectively, $p = 0.65$), mutations beginning at E746 trended towards more favorable survival. Median PFS was 15 months (95% CI: 11–37) in the E746 group versus. 10 months (95% CI: 5–13) in the L747 group ($p = 0.06$), and median OS was 48 months (95% CI: 25–not reached) versus 22 months (95% CI: 10–not reached) ($p = 0.07$; Supplementary Fig. 1).

Within the compound mutation group (n = 12), all cases included either a G719X (n = 5) or L858X mutation (n = 7). For this group overall, we observed an ORR of 67%, median PFS of 14 months (95% CI: 5–22), median TTD of 26 months (95% CI: 5–36), and median OS of 36 months (95% CI 20–46). The PFS range of compound mutations including G719X was 4.8 months to ongoing at 26.1 months, with a median PFS of 16 months (95% CI: 5–not reached). For compound mutations including L858X, PFS ranged from 1.1 months to 24.9 months with a median of 14 months (95% CI: 1–20).

Presence of brain metastasis at baseline was not found to be associated with worse outcomes in this cohort. Among cases without baseline brain metastases (n = 16), ORR was 63%, PFS was 11 months (95% CI: 10–25), TTD was 25 months (95% CI: 10–32), and OS was 35 months (95% CI: 20–50). Among cases with baseline brain metastases (n = 21), ORR was 86%, PFS was 13 months (95% CI: 8–15), TTD was 20 months (95% CI: 14–38), and OS was 39 months (95% CI: 22–51). In this group, 10 patients did not receive local therapy for brain metastasis before osimertinib start and had imaging available for review. Of these, the CNS response rate was found to be 80%, consistent with systemic response rates.

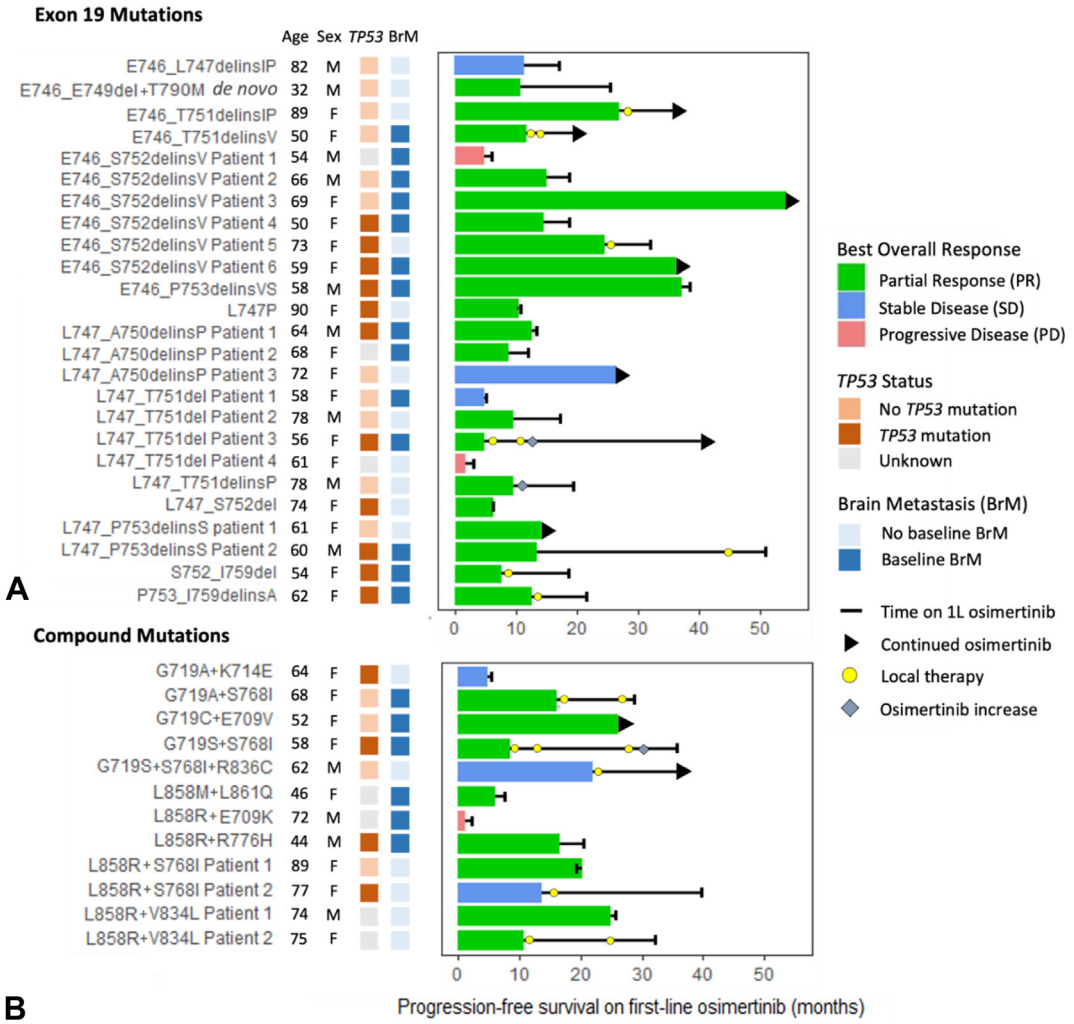


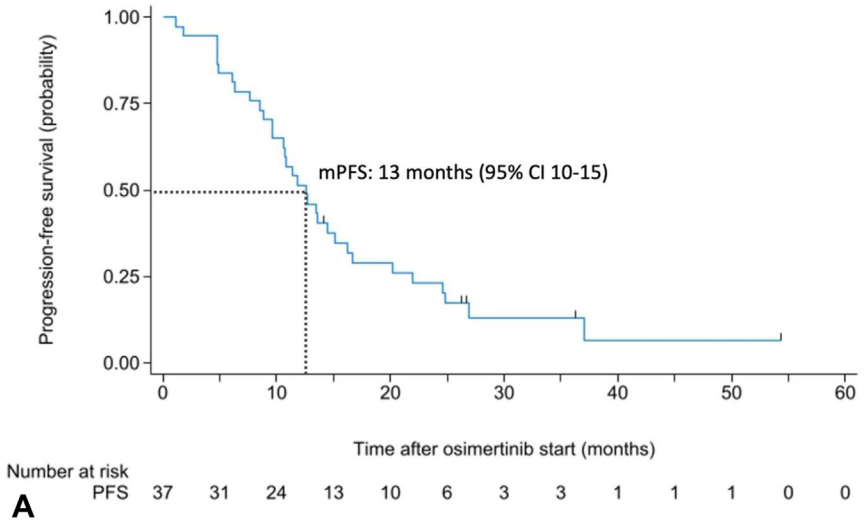
Figure 2. Outcomes and treatment course for patients with NSCLC harboring uncommon EGFR (*A*) exon 19 mutations and (*B*) compound mutations treated with first-line osimertinib. Colors of bars describe best overall response. Length of bars describe PFS on first-line osimertinib. Black lines describe the length of time each patient remained on osimertinib after progression. At the end of each line, vertical bars indicate discontinuation of first-line osimertinib, while arrows denote ongoing treatment at the completion of data collection. Symbols are included to denote local therapy events or osimertinib dose increase events for those who remained on osimertinib after disease progression. F, female; M, male.

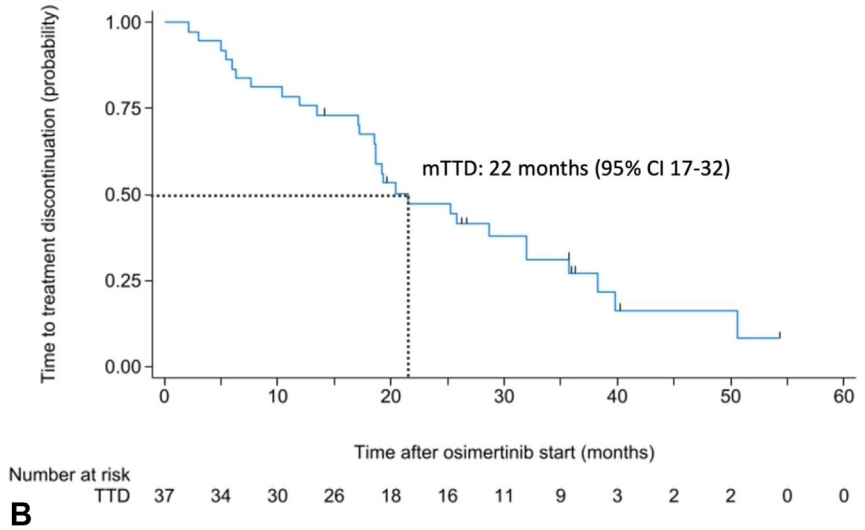
No differences in response or survival on first-line osimertinib were observed when stratifying by presence of a *TP53* co-mutation in this cohort. Cases negative for *TP53* co-mutations (n = 16) had an ORR of 73%, median PFS of 16 months (95% CI: 10–27), and median OS of 34 months (95% CI: 22–not reached), although cases positive for *TP53* (n = 15) had an ORR of 81%, median PFS of 13 months (95% CI 6–15), and median OS of 46 months (95% CI: 32–not reached).

Resistance Mutations and Subsequent Therapy

Repeat molecular testing after development of tumor resistance to osimertinib therapy was performed in 22 cases by means of tissue biopsy only (n = 9), liquid biopsy only (n = 9), or both (n = 4). Of these, putative acquired resistance mutations were identified in 13 cases (59%; Table 2). Four tumors acquired novel EGFR mutations, including C797S (n = 2). Additional genomic alterations identified on resistance included PIK3CA mutations (n = 3), CDKN2A/B loss (n = 2), MET amplification (n = 2), and CTNNB1 mutations (n = 2) (Table 2). Histologic transformation was not identified as a mechanism of resistance in any of the 13 tumors with tissue biopsy.

Eighteen patients received subsequent systemic therapy following progression on first-line osimertinib with duration of second-line therapy ranging from one to 14 months. Of these, the most common treatments included chemotherapy or chemotherapy with immunotherapy (n = 8), with duration of treatment ranging from three to 14 months. Six patients received chemotherapy in combination or in sequence with osimertinib





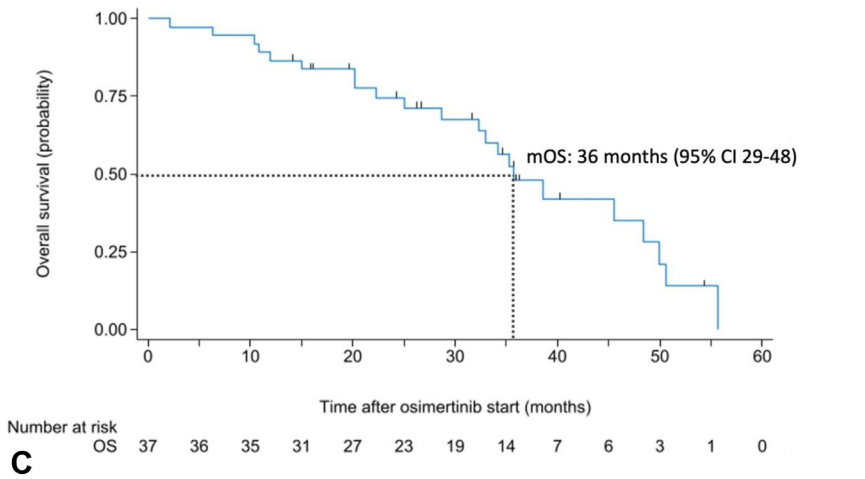


Figure 3. Kaplan-Meier analysis of (*A*) PFS, (*B*) TTD, and (*C*) OS in the overall cohort. CI, confidence interval; m, median; OS, overall survival; PFS, progression-free survival; TTD, time to treatment discontinuation.

Table 2. Acquired Resistance Mutations on First-Line Osimertinib

	Acquired Mutations				
Baseline EGFR mutation	EGFR	PIK3CA	MET	CDKN2A/B	CTNNB1
E746_L747delinsIP				CN loss	
E746_S752delinsV Patient 4	G724S				
E746_P753delinsVS		E542K			
L747_A750delinsP Patient 1		E542K			
L747_A750delinsP Patient 2	C797S				
L747_T751del Patient 2			CN amp		
S752_I759del					S37C
P753_I759delinsA	CN amp			CN loss	
G719A + K714E					
G719S + S768I					W383G
L858M + L861Q		E545K			
L858R + R776H			CN amp		
L858R + V834L Patient 2	C797S				

Note: Twenty-two patients underwent repeat molecular testing by means of tumor tissue biopsy or cell-free DNA liquid assay. Acquired mutations were identified in 13 cases listed.
CN, copy number; amp, amplification.

with duration ranging from one to 12 months. Three patients received investigational drugs including amivantamab and savolitinib. Nine patients received more than one line of subsequent systemic therapy. Subsequent lines of systemic therapy are detailed in Supplementary Table 1.

Discussion

The heterogeneity of uncommon EGFR mutations has made them challenging to study and ambiguous to treat. In this retrospective study, we describe the outcomes on first-line osimertinib for a cohort of 37 patients diagnosed with NSCLC harboring uncommon EGFR exon 19 mutations or EGFR compound mutations. These two distinct subtypes of uncommon mutations were selected for inclusion given more prevalent use of first-line osimertinib for patients with tumors harboring these mutation during the study period, as compared with other uncommon single mutations like G719X, S768I, and L861Q, and the relative under-emphasis of these specific groups in the contemporary osimertinib literature.[26–29] Overall, we observed an ORR of 76%, a median real-world PFS of 13 months, TTD of 22 months, and OS of 36 months. Although these results support consideration of first-line osimertinib in this patient population, we observed significant variation in outcomes on treatment, suggesting distinct biological and pharmacokinetic properties associated with different exon 19 and compound EGFR mutations.

Analyzing individual atypical exon 19 mutation subtypes highlights nuances in outcomes and responses to first-line osimertinib that may be otherwise masked by the predominance of E746_A750del when grouped together as 'exon 19 deletions.' Among 25 patients with tumors harboring 14 different rare exon 19 mutations, the ORR on osimertinib was robust at 80%, but there was significant heterogeneity in the durability of response as half of patients progressed within the first year on osimertinib. As a group, exon 19 deletion mutations are considered TKI sensitive, but the differences in amino acid sequence within the tyrosine kinase domain clearly impact activity of osimertinib.[15,30] Preclinical and in silico models have found the impact of sequence variation on structural features and function among exon 19 deletion variants including ATP binding, dimerization and autophosphorylation, and TKI binding affinity.[15,16,18]

With countless distinct and rarely-occurring EGFR exon 19 variants, there is significant clinical incentive to group them as prognostic and predictive biomarkers. We observed that atypical exon 19 mutations starting at codon E746 trended toward more favorable outcomes than those starting at L747. Alleles observed in more than one patient tumor certainly contribute to this trend, such as E746_S752delinsV (n = 6) with multiple durable responses beyond two years and L747_T751del (n = 4) with a maximum PFS of only 9.6 months. A few prior studies reported shorter survival with L747 mutations, though predominately in patients treated with first and second generation TKIs, noting that E746 mutations are associated with increased frequency of acquired T790M mutation compared with L747 mutations.[19,22,31] In addition, certain more prevalent variants such as L747_A750delinsP have been associated with inferior outcomes on first-line osimertinib as compared with the classic E746_A750del mutation with a median PFS of 11.7 months compared with 21.3 months, respectively,

in a recent large analysis.[30] Due to small numbers of patients with each variant and evolving patterns of TKI use in recent years, other grouping classifications based on nucleotide deletion length, structural conformation, or mutation prevalence have also proved difficult to replicate clinically.[18,22]

Whether alterations in the molecular conformation of any exon 19 variant led to enhanced sensitivity to second-generation TKIs like afatinib over third-generation TKIs like osimertinib is a key question with immediate clinical implications. For example, in cell lines and computational models, the L747_A750delinsP mutation demonstrates reduced sensitivity to erlotinib and osimertinib but remains highly sensitive to the second-generation TKI afatinib when compared with E746_A750del.[15,17] Truini et al.[17] describe steric hinderance caused by the proline insertion that uniquely impacts osimertinib binding, while afatinib maintains superior activity due in part to non-covalent interactions enabling enhanced interaction with the C797 side chain. Predictive models and preclinical assays have also suggested enhanced sensitivity to afatinib for other exon 19 variants including L747P, L747S, and T751_I759delinsN.[32]

Among EGFR compound mutations, we also observed favorable responses to first-line osimertinib, including in tumors containing canonically "TKI-resistant" mutations like G719X or S768I. G719X and S768I most often occur as de novo compound mutations rather than single mutations, often together, or with L858R, E709X, or L861Q.[33] In a structural classification of EGFR mutations, both of these uncommon mutations are considered putative P-loop and αC-helix compressing (PACC) mutations, in which changes in the P-loop orientation are expected to destabilize osimertinib binding.[32] Second-generation EGFR TKIs, such as afatinib, do not interact with the EGFR P-loop and are thus hypothesized to be more active for PACC mutations.[32] In focusing on compound mutations, we observed durable responses to osimertinib among several of these cases with putative compound PACC mutations, including one patient tumor harboring G719C + E709V who remained progression-free on first-line osimertinib for more than 26 months. Interestingly, according to the structural classification model, some mutations containing a classic mutation and an uncommon mutation are considered to behave like classic mutations (e.g., L858R + E709K), while others may behave like PACC mutations (e.g., L858R + S768I).[32]

Outcomes of osimertinib in small cohorts of G719X, L816Q, and S786I mutations(currently with Food and Drugs Administration, approval for afatinib) have been published in recent years and also contain small numbers of EGFR compound mutations with variable durations of response.[26–29] The largest group of 18 EGFR compound mutations from the prospective phase II UNICORN study includes eight compound PACC mutations, all G719X with either S786I or E709X, all achieving disease control with first-line osimertinib and PFS ranging from around four months to ongoing past 24 months.[27] Among 20 G719X mutant tumors in this study, response rate was higher for compound mutations than for G719X mutations occurring alone. Each permutation of uncommon EGFR compound mutations likely has unique pharmacokinetic properties, with varied pairs of mutation sites and encompassing a variety of substitutions at the same codon, such that G719C + S768I may be distinct from both G719C + E709X and G719S + S768I. The summarized rates of response and survival across groups of various non-classical EGFR mutations in this study and others we describe differ widely based on the mutations represented, underscoring the pitfalls of grouping together all uncommon EGFR mutations.[26–29] The extensive scope of possible compound mutations and their relative infrequency means that continued reporting of collected cases and outcomes is needed to identify clinical patterns and guide practice.

Furthermore, our observation of heterogeneous responses even among cases with the same uncommon EGFR mutation emphasizes the presence of other tumor intrinsic factors driving outcomes. For example, among the six tumors harboring the exon 19 E746_S752delinsV mutation, the PFS ranged from 4.8 months to 4.5 years. Although studies have identified the presence of a *TP53* mutation as one such factor, we did not observe a statistically significant difference when stratifying by *TP53* co-mutation status in this small group.[34]

The presence of brain metastasis at baseline was also not found to be associated with worse outcomes in this cohort. Osimertinib has high CNS penetrance with CNS response rate of 91% among the classical EGFR mutations included in the FLAURA study.[35] However, CNS outcomes in patients with atypical EGFR mutations are lesser known. One retrospective study reported an intracranial response rate of 46% with osimertinib among 16 patients with diverse uncommon EGFR mutations.[26] In our cohort, we observed a CNS response rate of 80% among 10 patients with brain metastases at baseline who did not receive local therapy to the brain before the initiation of osimertinib and had imaging available for review. The robust intracranial response observed is likely a factor underlying the lack of prognostic significance of baseline brain metastases in this study, but the small number of patients assessed limits conclusions from this finding.

Of the 22 patients in our cohort who underwent repeat molecular testing after progression on first-line osimertinib, presumed dominant acquired resistance mutations were identified in 13 cases. These mutations

are consistent with EGFR-dependent and independent mechanisms of resistance, including EGFR C797S and c-MET amplification.[36–38] Interestingly, histologic transformation to small cell or squamous cell phenotypes (which has been noted in up to 14% of tumor samples after treatment with osimertinib) was not identified as a mechanism of resistance for any of the 13 tumors with tissue assessed.[38] It is likely that alterations in TKI affinity can impact tumor evolutionary pressures that drive different mechanisms of resistance among individual EGFR variants, which could inform treatment strategy in the future.

Regarding treatment modalities utilized after progression on first-line osimertinib, 12 patients in this cohort were able to remain on first-line osimertinib for 8 to 37 months after progression with the addition of local therapy. For EGFR variants that are less sensitive and develop earlier resistance to osimertinib, the incorporation of local therapy for oligoprogressive disease can offer more durable disease control and longer time on TKI therapy.

A primary limitation of this investigation, inherent in the study of rare mutations, is the small size of the cohort and heterogeneity of mutations included, with few mutations represented in more than one patient tumor. The retrospective and real-world nature of the study also contributes to significant variation, such as timing of response assessments, use of local therapies post-progression, and utilization of genetic sequencing panels of varying breadth to identify baseline co-mutations or acquired resistance mutations over the course of the study.

In conclusion, this study contributes to the characterization of the efficacy of first-line osimertinib for patients with NSCLC harboring uncommon EGFR exon 19 mutations and compound mutations. Our results overall support the use of first-line osimertinib in this patient population, but also highlight the heterogeneity and unique responses to treatment that exist among this group. Widespread collaborative efforts are needed to compile data for each specific uncommon mutation to better understand their natural history and unique responses to treatment, and to ultimately hone our precision approach beyond just E746_A750del and L858R mutations.

CRediT Authorship Contribution Statement

Tia Cheunkarndee: Conceptualization, Methodology, Formal analysis, Investigation, Data curation, Writing - original draft, Visualization, Project administration.

Matthew Z. Guo: Methodology, Investigation, Data curation, Writing - review and editing.

Stefanie Houseknecht: Resources, Writing - review and editing.

Josephine L. Feliciano: Writing - review and editing.

Christine L. Hann: Writing - review and editing.

Vincent K. Lam: Writing - review and editing.

Benjamin P. Levy: Writing - review and editing.

Joseph C. Murray: Writing - review and editing.

Julie R. Brahmer: Writing - review and editing.

Patrick M. Forde: Writing - review and editing.

Kristen A. Marrone: Conceptualization, Methodology, Writing - review and editing.

Susan C. Scott: Conceptualization, Methodology, Visualization, Validation, Writing - review and editing, Supervision.

Disclosures

Dr. Houseknecht has been consulting for AstraZeneca, Aptar Pharma, and has stock ownership with Pfizer. Dr. Feliciano has received research funding direct to the institution from AstraZeneca, Pfizer, Bristol Myers Squibb and was consulting for Regeneron, AstraZeneca, Coherus, Eli Lilly, Genentech, Takeda, Jansen, Daiichi Sankyo. Dr. Hann has received research funding direct to the institution from AstraZeneca, Amgen, Daiichi, Bristol Meyers Squibb, AbbVie; and personal fees from AstraZeneca, Puma BioTechnology, Daiichi, Janssen and Bristol Meyers Squibb. Dr. Lam was consulting for Iovance Biotherapeutics, Anheart Therapeutics, Takeda, Seattle Genetics, Bristol Myers Squibb, AstraZeneca, and Guardant Health; and has received research funding direct to the institution from GlaxoSmithKline, Bristol Myers Squibb, AstraZeneca, Merck and Seattle Genetics. Dr. Levy has received personal fees from AstraZeneca, Novartis, Eli Lilly, Genentech, Pfizer, Guardant 360, Takeda, Bristol Meyers Squibb, Novocure, Janssen, Daiichi Sankyo, Merck. Dr. Murray has received personal fees from Regeneron, Johnson & Johnson. Dr. Brahmer has received personal fees from Roche, grants and personal fees from Bristol Meyers Squibb, grants from Merck, personal fees from Regeneron, grants and personal fees from AstraZeneca, personal fees from Amgen, personal fees from Summit, personal fees from Mestag, grants and personal fees from RAPT therapeutics, personal fees from GlaxoSmithKline, and personal fees from Sanofi.Dr.Forde has received research funding direct to the institution from AstraZeneca, BMS, Novartis, Regeneron, BioNTech; consulting fees from Ascendis, AstraZeneca, BMS, Curevac, Novartis, Regeneron, G1, Genelux, Genentech, Gritstone, Merck, Janssen, F Star, Sanofi, Amgen, Fosun, Teva, Synthekine, Flame, Iteos, Tavotek, Teva; and has DSMB membership for Polaris. Dr. Marrone has been consulting for AstraZeneca, Amgen, Janssen, Mirati Therapeutics, Daiichi Sankyo/Lilly and Puma Biotechnology; and has received honoraria from AstraZeneca,

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Supplementary Data

Note: To access the supplementary material accompanying this article, visit the online version of the *JTO Clinical and Research Reports* at www.jtocrr.org and at [https://doi.org/10.1016/j.jtocrr.2024.100686].

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