ORIGINAL ARTICLE

UNcommon EGFR Mutations: International Case Series on Efficacy of Osimertinib in Real-Life Practice in First-LiNe Setting (UNICORN)

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Disclosure: Dr. Bar declares receiving consulting fees from Merck Sharp & Dohme, Bristol-Myers Squibb, Roche, AstraZeneca, Novartis, Pfizer, Causalis, Bayer, and Takeda, and research grants from AstraZeneca, Takeda, OncoHost, Pfizer, ImmuneAI, Merck Sharp & Dohme, Roche, and Eli Lilly, all for the institute. Dr. Peled reports receiving grants and personal fees from AstraZeneca, Bayer, Boehringer Ingelheim, Bristol-Myers Squibb, Eli Lilly, FoundationMedicine, Gaurdant360, Merck, Merck Sharp & Dohme, Novartis, NovellusDx, Pfizer, Roche, and Takeda. Dr. Wollner reports receiving personal fees from Roche, AstraZeneca, Bristol-Myers Squibb, Merck Sharp & Dohme, Novartis, Pfizer, Takeda, and Merck Serono. Dr. Girard reports receiving grants and personal fees from Bristol-Myers Squibb, Merck Sharp & Dohme, Roche, Novartis, AstraZeneca, Janssen, Pfizer, Sanofi, Eli Lilly, and Amgen; receiving grants from Boehringer Ingelheim, BeiGene, and Daiichi Sankyo, all outside the submitted work; and having a family member who is an employee of AstraZeneca. Dr. Patel declared having scientific advisory income from Amgen, AstraZeneca, Bristol-Myers Squibb, Certis, Eli Lilly, Genentech, Illumina, Merck, Pfizer, Rakuten, and Tempus; and receiving research funding for the institute from Amgen, AstraZeneca/MedImmune, Bristol-Myers Squibb, Eli Lilly, Fate Therapeutics, Iovance, Merck, Pfizer, Roche/Genentech, and SQZ Biotechnologie. Dr. Zer reports receiving grants from Bristol-Myers Squibb; and personal fees from Roche, AstraZeneca, Merck Sharp & Dohme, Takeda, Novartis, Stebafrom, and Nixio, all outside of the submitted work. Dr. Moskovitz reports receiving honoraria from Roche, Takeda, AstraZeneca, Bristol-Myers Squibb, Merck Sharp & Dohme, and Novartis. Dr. Rottenberg reports receiving personal fees from Merck Sharp & Dohme, Roche, Novartis, AstraZeneca, Pfizer, Sanofi, and Medison. Dr. Calles reports receiving personal fees from AstraZeneca, Bayer, Pfizer, Roche, Novartis, Bristol-Myers Squibb, Takeda, Sanofi, and Boehringer Ingelheim; and grants and personal fees from Merck Sharp & Dome. Dr. Hochmair reports receiving personal fees and nonfinancial support from AstraZeneca, Boehringer Ingelheim, Takeda, and Roche; and personal fees from Merck Sharp & Dohme. Dr. Reck reports receiving personal fees from Amgen, AstraZeneca, BeiGene, Boehringer Ingelheim, Bristol-Myers Squibb, Eli Lilly, Mirati, Merck, Merck Sharp & Dohme, Novartis, Pfizer, Roche, and Sanofi. Dr. Rodriguez reports receiving personal fees from AstraZeneca and Bristol-Myers Squibb from Novartis, Jansen, Genentech, Targeted Oncology, and Research to Practice. Dr. Bettini reports receiving personal fees from Merck Sharp & Dohme, Janssen, and Merck. Dr. Häfliger reports receiving advisory fees from AstraZeneca. Dr. Addeo declares having consulting or advisory role for Bristol-Myers Squibb, AstraZeneca, Boehringer Ingelheim, Roche, Merck Sharp & Dohme, Pfizer, Eli Lilly, Astellas, Takeda, and Amgen; and serving on the speaker bureau of Eli Lilly and AstraZeneca. All the reported institutions are not related to the work in this manuscript. The remaining authors declare no conflict of interest.

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ISSN: 1556-0864

https://doi.org/10.1016/j.jtho.2022.10.004

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Received 30 March 2022; revised 10 September 2022; accepted 3 October 2022
Available online - 25 October 2022

ABSTRACT

Introduction: Approximately 10% of EGFR mutations (EGFRmuts) are uncommon (ucEGFRmuts). We aimed to collect real-world data about osimertinib for patients with ucEGFRmuts.

Methods: This is a multicenter, retrospective study of ucEGFRmut (exon 20 insertions excluded) metastatic NSCLC treated with osimertinib as first EGFR inhibitor. The Response Evaluation Criteria in Solid Tumors and response assessment in neuro-oncology brain metastases brain objective response rate (ORR) were evaluated by the investigators. Median progression-free survival (mPFS), median overall survival, and median duration of response (mDOR) were calculated from osimertinib initiation. Mutations found at resistance were collected.

Results: A total of 60 patients were included (22 centers, nine countries), with median age of 64 years, 75% females, and 83% Caucasian. The largest subgroups were G719X (30%), L861Q (20%), and de novo Thr790Met (T790M) (15%). The ORR was 61%, mPFS 9.5 months, mDOR 17.4 months, and median overall survival 24.5 months. Regarding patients with no concurrent common mutations or T790M (group A, n = 44), ORR was 60%, mPFS 8.6 months, and mDOR 11 months. For G719X, ORR was 47%, mPFS 8.8 months, and mDOR 9.1 months. For L861Q, ORR was 80%, mPFS 16 months, and mDOR 16 months. For de novo T790M, ORR was 44%, mPFS 12.7 months, and mDOR 46.2 months. Compound EGFRmut including common mutations had better outcome compared with only ucEGFRmut. For 13 patients with a response assessment in neuro-oncology brain metastases–evaluable brain metastases, brain ORR was 46%. For 14 patients, rebiopsy results were analyzed: four patients with additional EGFR mutation (C797S, D585Y, E709K), three with new TP53 mutation, one with c-Met amplification, one with PIK3CA mutation, and one with neuroendocrine transformation.

Conclusions: Osimertinib was found to have an activity in ucEGFRmut with a high rate of disease control systemically and intracranially. Several resistance mechanisms were identified. This report comprises, to the best of our knowledge, the largest data set of its kind.

Keywords: NSCLC; Metastatic; Uncommon EGFR mutation; Compound mutations

Introduction

EGFR tyrosine kinase inhibitors (TKIs) are considered the standard first-line treatment options for patients with advanced or metastatic NSCLC harboring sensitizing EGFR mutations.[1] A number of phase 3 trials revealed superior objective response rate (ORR) and progression-free survival (PFS) for EGFR TKIs compared with platinum-based doublet chemotherapy.[2] Recently, the FLAURA trial has revealed that the third-generation TKI, osimertinib, is superior to first-generation TKIs, erlotinib and gefitinib, in terms of PFS and overall survival (OS).[3]

Osimertinib is an oral, third-generation, irreversible EGFR TKI that selectively inhibits both sensitizing EGFR mutations and Thr790Met (T790M) resistance mutations.[4] Osimertinib is approved for the treatment of patients with metastatic NSCLC harboring specific EGFR mutation exon 19 deletion or exon 21 Leu858Arg mutation (L858R)[3] and for patients positive for T790M resistance mutation after progression on earlier generation EGFR TKIs.[5] Previous studies highlight the central nervous system (CNS) activity of osimertinib with efficacy superior to that of first-generation EGFR TKIs and platinum-based chemotherapy.[6]

The common EGFR mutations account for 75% to 80% of EGFR mutations in NSCLC.[7] The uncommon

mutations represent the remainder of the EGFR mutations and include a highly heterogeneous group of molecular alterations within exons 18 to 21.[8] The widespread use of next-generation sequencing has increased the likelihood to detect these uncommon mutations. Aside from exon 20 insertions, the most prevalent uncommon EGFR mutations (ucEGFRmuts) include G719X (including G719S, G719A, G719C, and G719D substitutions), S768I, and L861Q, in exons 18, 20, and 21, respectively, which have been collectively referred to as the major uncommon mutations.[8,9]

The available data are still rather unclear regarding the clinical efficacy of EGFR TKIs for NSCLC with ucEGFRmut. Response rates to EGFR TKIs in patients with NSCLC with sensitizing EGFR mutations (exon 19 deletions or L858R) range approximately from 60% to 80%,[2] whereas data regarding the efficacy of first- or second-generation TKIs in patients with NSCLC ucEGFRmut are inconsistent, on the basis of retrospective or post hoc analyses. For example, in the NEJ002 trial, the ORR and median PFS (mPFS) with gefitinib were significantly lower in patients with ucEGFRmuts in comparison with those with common sensitizing EGFR mutations (20% versus 76%; 2.2 mo versus 11.4 mo).[10] In a different study, Wu et al.[11] reported that ORR to first-generation TKIs, gefitinib or erlotinib, was 57.1% in patients with G719X or L861Q mutations, with a mPFS of 6.0 months. A post hoc analysis on afatinib efficacy from the LUX-Lung 2, LUX-Lung 3, and LUX-Lung 6 trial populations revealed an ORR of 71% with a mPFS of 11 months for patients harboring ucEGFRmut.[12] The only outliers were the patients with T790M or exon 20 insertion mutations who had a poor ORR and short mPFS (ORR 9%–14% and mPFS $<$ 3 mo). A larger report including also data from expanded-access programs and phase 3b studies identified 315 TKI-naive, afatinib-treated patients with ucEGFRmut.[13] For 101 patients with S768I, G719X, or L861Q, time-to-treatment failure (TTF) was 10.8 months and the RR was 60%. On the basis of these findings, the Food and Drug Administration and the European Medicines Agency have approved afatinib for patients with NSCLC with any sensitizing EGFR mutation.[14]

So far, the only prospective data on osimertinib efficacy come from the KCSG-LU15-09 phase 2 study, performed in Korea.[15] Cho et al.[15] reported an ORR of 50% and a mPFS of 8.2 months (median OS [mOS] was not reached) among a total of 36 patients harboring ucEGFRmut treated with osimertinib (as first or later lines of treatment). In addition, a U.S. real-world study reported on 20 patients with ucEGFRmut receiving first-line osimertinib,[16] with a median time on treatment of 8.9 months. These studies excluded patients with a common concomitant EGFR mutation. To further clarify the impact and benefit of osimertinib in patients harboring an ucEGFRmut, we have launched an international retrospective study of the efficacy of osimertinib in real-life practice in first-line setting (UNICORN study).

Materials and Methods

Study Design

The UNICORN study was an academic-initiated and sponsored, multicenter, real-world retrospective study. Patients included had advanced NSCLC with ucEGFRmut, including atypical exon 19 deletions (i.e., deletions-insertions) and excluding exon 20 insertion mutations. Common mutations, L858R, and common exon 19 deletions were also included as a part of compound mutations when found together with uncommon mutations. Patients must have received osimertinib as the first EGFR TKI for their advanced disease. To include only patients with reasonable follow-up, osimertinib must have been initiated no later than the end of January 2021.

Procedures

The study was conducted in 22 centers in nine different countries. Patients were identified by retrospective screening of the local patients' database of each institute. Data were retrieved from the patients' charts by the local investigators. The Response Evaluation Criteria in Solid Tumors version 1.1 response and response assessment in neuro-oncology brain metastases (RANO-BM) were evaluated by the investigators. Treatment lines administered before osimertinib were counted as for advanced disease if completed 6 months or less before the diagnosis of advanced disease. Radiotherapy treatments were categorized as ablative, palliative, whole brain radiotherapy and brain stereotactic radiosurgery. All data were anonymized before their transfer to the lead authors for joint analysis. Data cutoff date was September 17, 2021.

Statistical Analysis

Data analysis was of descriptive nature, with mean and 95% confidence interval for continuous variables (by Wilson score interval) and percentages and range for categorical variables. The PFS and OS were calculated by Kaplan-Meier method from initiation of osimertinib, and duration of response (DOR) was calculated for the responders. Exploratory analyses and comparisons between different molecularly defined subgroups were performed.

Role of the Funding Source

The study was supported by AstraZeneca. Support consisted of funding a data manager, statistical support, and figure preparation. AstraZeneca employees were

Table 1. Patient Characteristics

Characteristics	All Study Cohort (N = 60)	Group A: Uncommon Mutations Only (n = 44)	Group B: Common With Uncommon Mutations (n = 16)
Age (median, range), y	64 (35-91)	63 (35-85)	68 (49-91)
Females, n (%)	45 (76)	35 (80)	10 (63)
Histology, n (%)			
Adenocarcinoma	58 (97)	43 (98)	15 (94)
Other	2 (3)	1 (2)	1 (6)
Ethnicity, n (%)			
Caucasian	50 (83)	38 (86)	12 (75)
Asian	4 (7)	3 (7)	1 (6)
Hispanic	3 (5)	1 (2)	2 (13)
Unknown	3 (5)	2 (5)	1 (6)
Smoking status, n (%)			
Never	29 (48)	21 (48)	8 (50)
Past	23 (38)	17 (39)	6 (37)
Current	7 (12)	6 (14)	1 (6)
Unknown	1 (2)	0	1 (6)
Duration of advanced disease at osimertinib initiation, median, 95% CI, mo	1.3 (2.4-7.6)	1.3 (1.5-7.9)	1.6 (1.2-10.5)
Treatments for early disease, n (%)			
Surgery	5 (8)	4 (80)	1 (50)
Adjuvant chemotherapy	1 (2)	1 (20)	0
Chemoradiation	2 (3)	1 (20)	1 (50)
Immunotherapy[a]	1 (2)	0	1 (50)
Number of treatment lines for advanced disease before osimertinib, n (%)			
None	53 (88)	39 (89)	14 (88)
One	6 (10)	4 (9)	2 (12)
Two	1 (2)	1 (2)	0
Treatments for advanced disease before osimertinib, n (%)			
Chemotherapy	5 (8)	4 (9)	1 (6)
Chemoimmunotherapy	1 (2)	1 (2)	0
Chemoradiation	2 (3)	1 (2)	1 (6)
None	52 (87)	38 (86)	14 (88)
Sites of metastasis at initiating osimertinib, n (%)			
Brain	23 (38)	20 (45)	3 (19)
Bone	26 (43)	22 (50)	4 (25)
Liver	2 (3)	2 (5)	0
Lung/pleura	29 (48)	21 (48)	8 (50)
Radiotherapy treatments for advanced disease, n (%)			
Palliative	19 (32)	17 (39)	2 (13)
SRS	9 (15)	6 (14)	3 (19)
Ablative	4 (7)	4 (9)	0
WBRT	1 (2)	1 (2)	0
ECOG PS at initiation of osimertinib, n (%)			
0	21 (34)	14 (32)	7 (44)
1	30 (50)	25 (57)	5 (31)
2	5 (8)	3 (7)	2 (13)
3	2 (3)	1 (2)	1 (6)
4	1 (2)	1 (2)	0
UK	1 (2)	0	1 (6)
Sites of progression on osimertinib, n (%)			
Systemic	27 (45)	22 (50)	5 (31)
Brain	5 (8)	4 (9)	1 (6)
Systemic and brain	7 (12)	6 (14)	1 (6)

(continued)

Table 1. Continued

Characteristics	All Study Cohort (N = 60)	Group A: Uncommon Mutations Only (n = 44)	Group B: Common With Uncommon Mutations (n = 16)
Reason for stopping osimertinib treatment, n (%)			
PD or death	33 (55)	27 (61)	6 (38)
Toxicity	3 (5)	3 (7)	0
Other	3 (5)	2 (4)	1 (6)
Treatment ongoing at data cutoff	21 (35)	12 (27)	9 (56)

Note: Percentages were rounded to whole numbers. Because of rounding and patients in more than one category, percentages may not be always add up to 100%.

[a]Durvalumab after chemoradiation.

CI, confidence interval; ECOG PS, Eastern Cooperative Oncology Group performance status; PD, progressive disease; SRS, stereotactic radiosurgery; UK, unknown; WBRT, whole brain radiotherapy.

involved in discussions regarding the study design and collection of the data but were not involved in discussions about the analysis, interpretation of the data, writing of this manuscript, and the decision to publish the results.

Ethics

Each participating center secured approval from the local ethics committee. Informed consent was obtained from all participants except in institutes whose ethics committee granted waivers from informed consent for retrospective data analysis. The study is registered at the National Institutes of Health clinical trials registry (NCT05421936).

Results

Patients

Data were transferred for joint analysis regarding 65 patients, with five of them excluded (initiation of osimertinib after the cutoff data, n = 1; exon 20 insertion, n = 2; missing data, n = 2). The characteristics of the 60 included patients are summarized in Table 1. Of the included patients, 15 had compound mutations including a common mutation (L858R or a common exon 19 deletion) or a de novo T790M mutation. One additional patient had only de novo T790M mutation. Because such patients can be expected to be more responsive to osimertinib, they were designated as group B (n = 16) and are presented and analyzed in parallel to the patients with no common mutations and no T790M mutation (group A, n = 44; Table 1). No significant differences were found between groups A and B in the characteristics included in Table 1 besides a trend for higher age for group B ($p = 0.05$ and data not shown). Regarding all the study cohorts, most patients were females with adenocarcinoma, never or past smokers. Seven patients (12%) were initially diagnosed with having early disease. Osimertinib was administered as the first-line treatment for advanced disease in 53 patients (88%); seven patients received other treatments before osimertinib for advanced disease: chemotherapy (five patients, 8%), chemoimmunotherapy (one patient, 2%), or chemoradiotherapy (two patients, 3%) treatments. One patient started osimertinib at a dose of 40 mg, and all others started with 80 mg dose. At initiation of osimertinib, 23 patients (38%) had brain metastasis. Most patients (51, 85%) had an Eastern Cooperative Oncology Group performance status of 0 to 1 at osimertinib initiation. Most were Caucasian (50, 83%). The largest subgroups of the included mutations were G719X (18 patients, 30%), L861Q (12 patients, 20%), and de novo T790M (nine patients, 15%). Six uncommon variants of exon 19 deletions were included as uncommon mutations[17] (Supplementary Table 1). Compound EGFR mutations were found in 27 patients (45%), and TP53 mutations were found in 21 patients (35%). Programmed death-ligand 1 immunohistochemistry results were available for 55 patients; of these, 24 (44%) were negative (<1% positive tumor cells), 20 (36%) were weakly positive (1%–49% positive tumor cells), and 11 (18%) were strongly positive (50% or more positive tumor cells).

Treatment Efficacy

Best response to osimertinib, as assessed by the treating physicians per Response Evaluation Criteria in Solid Tumors version 1.1, was available for 51 patients (85%). Among these 51 patients with assessable or measurable disease, complete response (CR) was reported in four patients (8%; 95% confidence interval [CI]: 3%–18%, group A—one [2%], group B—three [23%]), partial response (PR) in 27 patients (53%; 95% CI: 39%–66%, group A—22 [58%], group B—five [38%]), stable disease (SD) in 16 patients (31%; 95% CI: 20%–45%, group A—11 [29%], group B—five [38%]), and progressive disease (PD) in four patients (8%; 95% CI: 3%–18%, all in group A [10%]). ORR was similar between groups A (60%) and B (61%) (Table 2). Figure 1*A* and Supplementary Figure 1 illustrate the changes in tumor size, timing of maximal response, and details of the mutations. DOR is demonstrated qualitatively by the swimmer's plot (Fig. 1*B*). Median time to

Table 2. Efficacy of Osimertinib in Various Subgroups

Patient Subgroups	n (% of 60)	RR[a] (95% CI)	PFS, mo (95% CI)	OS, mo (95% CI)	DOR, mo (95% CI)
All patients	60 (100)	61 (47-73)	9.5 (8.5-17.4)	24.5 (17.4-35.1)	17.4 (9.1-NA)
Group A: only uncommon	44 (73)	60 (45-74)	8.6 (7.3-13.5)	22.1 (13.5-NA)	11.0 (9.0-NA)
Group B: uncommon with L858R/del19[b]/T790M	16 (27)	61 (35-82)	30.0 (12.7-NA)	31.4 (14.7-NA)	46.2 (30.7-NA)
G719X	18 (30)	47 (26-69)	8.8 (7.9-NA)	NA (17.4-NA)	9.1 (8.6-NA)
G719X, group A	16 (27)	53 (30-75)	8.6 (6.9-NA)	18.4 (10.2-NA)	9.1 (8.6-NA)
L861Q	12 (20)	80 (49-94)	16 (11-NA)	26.3 (22.1-NA)	16 (11-NA)
L861Q, group A	11 (18)	78 (45-94)	15.7 (8.9-18.8)	25.9 (21.8-NA)	16.0 (9.0-NA)
T790M	9 (15)	44 (19-73)	12.7 (9.5-NA)	NA (12-NA)	46.2 (3.8-NA)
TP53 mutant	21 (35)	60 (36-80)	8.5 (6.8-22.1)	26.3 (13.5-NA)	9.0 (7.9-NA)

Note: The largest EGFR mutational subgroups are represented. G719X-group A and L861Q-group A indicate patients with a G719X or L861Q mutation, respectively, and no concomitant L858R, common exon 19 deletion, or T790M.
[a]Of patients with assessable disease.
[b]Common exon 19 deletion mutations (i.e., G746_A750del, L747_T751del).
CI, confidence interval; del19, deletion exon 19; DOR, duration of response; NA, not applicable; OS, overall survival; PFS, progression-free survival; L858R, Leu858Arg mutation; RR, response rate; T790M, Thr790Met.

maximal response in group A was 2.9 months (95% CI: 2.7–5.2) and 3.0 months in group B (95% CI: 1.9–7.3).

At data cutoff, osimertinib treatment was ongoing for 21 patients (35% of the entire cohort). Among these 21 patients, for six (10% of the entire cohort), the treatment was ongoing beyond progression on osimertinib (group A—five, group B—one). There were 31 patients (52%) alive at data cutoff (group A—21 [48%], group B—10 [62%]). Median OS was 24.5 months (95% CI: 17.4–35.1 mo). The OS in groups A and B was 22.1 months and 31.4 months, respectively. An exploratory hazard ratio calculated comparing OS of these groups was 0.55 (95% CI: 0.22–1.36, $p = 0.19$; Fig. 2*A*). Median PFS was 9.5 months (95% CI: 8.5–17.4 mo). The PFS in groups A and B was 8.6 and 30.0 months, respectively (hazard ratio = 0.24 [95% CI: 0.09–0.63], $p = 0.0017$; Fig. 2*B*). Median DOR was 17.4 months (95% CI: 9.1–not applicable). The DOR for groups A and B was 11.0 and 46.2, respectively ($p = 0.026$; Fig. 2*C*).

Response, PFS and OS for Various Mutation Subgroups

We next evaluated the efficacy according to the specific EGFR mutation found. We focused on the subgroups of mutations of which a reasonable group had assessable

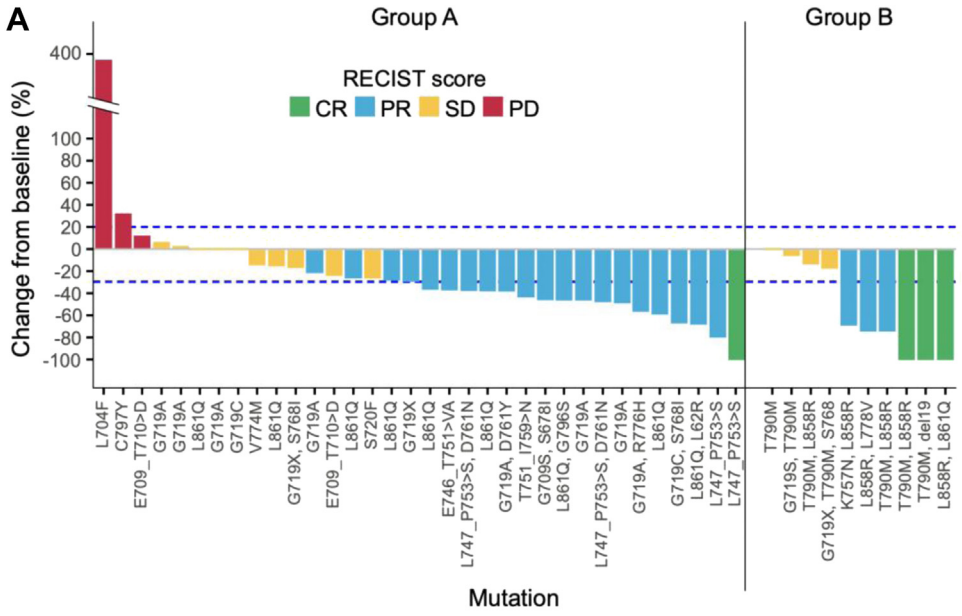

Figure 1. Response to osimertinib. (*A*) Waterfall plot of the maximal change in size. Mutations in the EGFR gene are noted below each bar (n = 44; for 16 patients maximal response data are missing, 10 from group A and six from group B). (*B*) Swimmer's plot of 60 patients, arranged by time on treatment. CR, complete response; PD, progressive disease; PR, partial response; SD, stable disease.

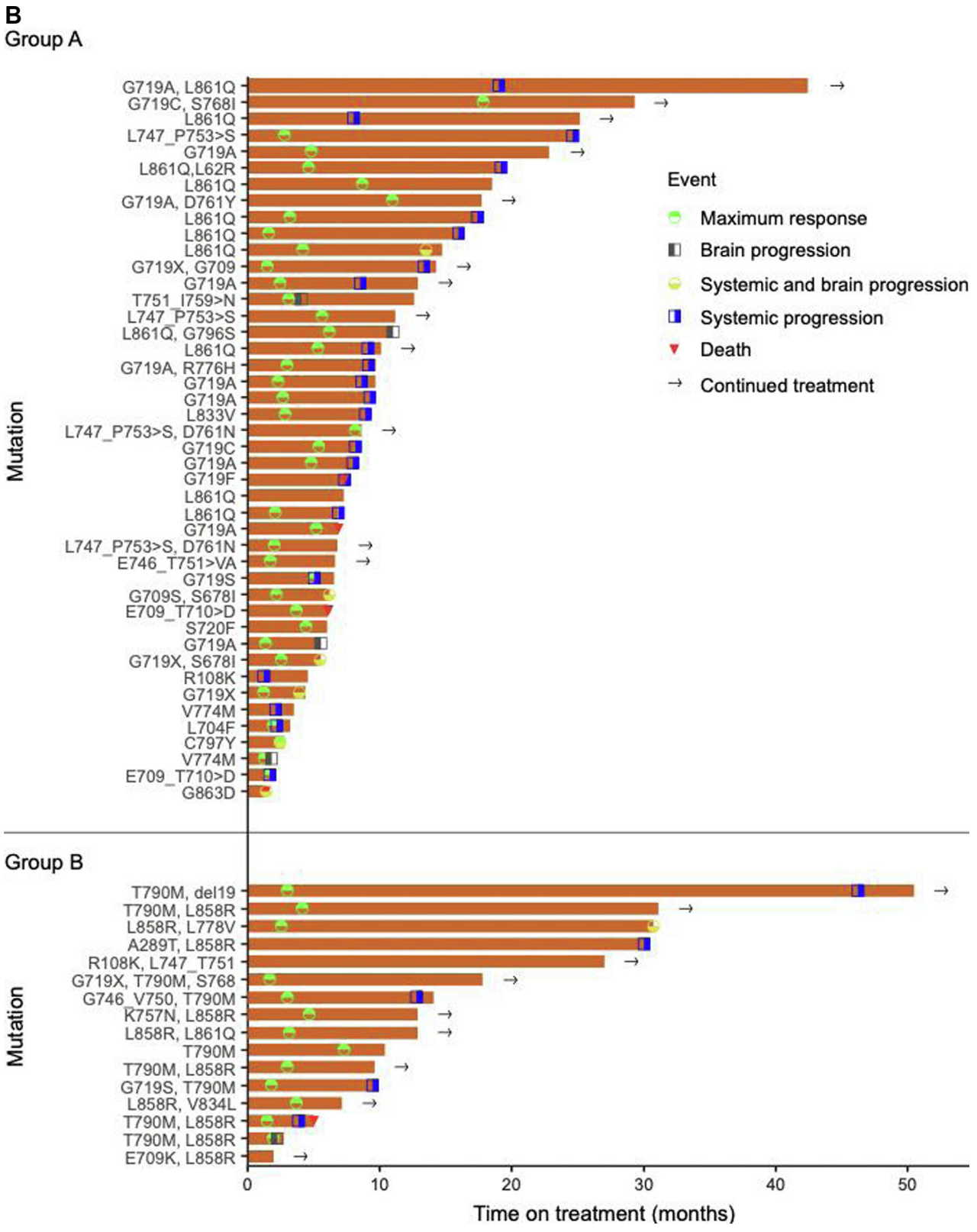

Figure 1. (*continued*)

disease. Table 2 demonstrates the response, PFS, OS, and DOR by mutation, including G719X, L861Q, and de novo T790M. Because 21 patients were found to have a TP53 co-mutation, this group was also analyzed separately. The results of groups A and B are reported, including those of subgroup A of each G719X and L861Q (i.e., cases

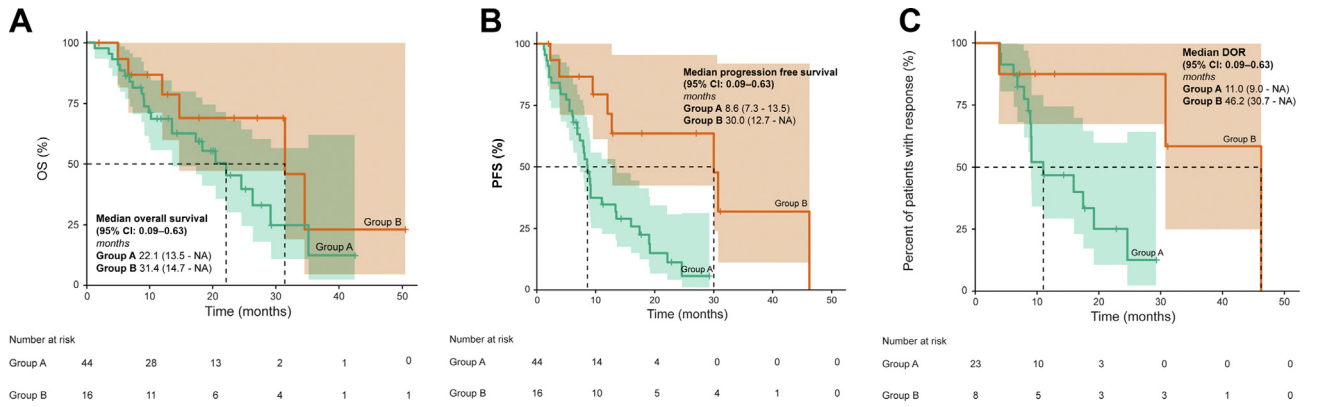

Figure 2. OS (*A*), PFS (*B*), and (*C*) DOR of osimertinib-treated patients. Data are represented for group A (only uncommon mutations) and group B (uncommon compound with common or T790M). Kaplan-Meier analysis. Exploratory comparison of groups A and B; for OS—HR = 0.55 (95% CI: 0.22-1.36, $p = 0.19$), for PFS—HR 0.24 (95% CI: 0.09-0.63, $p = 0.0017$). Median follow-up of the patients for OS analysis was 20.4 months (95% CI: 17.9-29.3) and for PFS analysis was 22.0 months (95% CI: 17.7-NA), and did not differ significantly between groups A and B. CI, confidence interval; HR, hazard ratio; NA, not applicable; OS, overall survival; PFS, progression-free survival.

that do not harbor concomitant common mutation or de novo T790M). The DCR was 100% in all these subgroups besides G719X where one case of PD was seen, including in the TP53 subgroup where two cases of PD were reported. The ORR was compared for each of the groups to the rest of the cohort, and no significant differences were found (data not shown).

To further characterize the efficacy of osimertinib in the various mutation subgroups, each of the mutation subgroups was compared in terms of PFS and OS to all of the other patients in the cohort (Supplementary Fig. 2). None of the comparisons were significant regarding OS. The mPFS was longer with a p value less than 0.05 for compound mutations including typical exon 19 deletion or L858R and for group B as a whole (in each case compared with the rest of the study cohort). No corrections for multiple comparisons were done in this exploratory analysis.

Brain Efficacy

There were 23 patients (38% of the cohort, 95% CI: 26%–52%; group A—20 [45%], group B—three [20%]) who had brain metastasis at presentation. For 16 patients, brain response was assessable, indicating measurements were available at initiation of osimertinib and at maximal response (Fig. 3). Regarding the radiologic

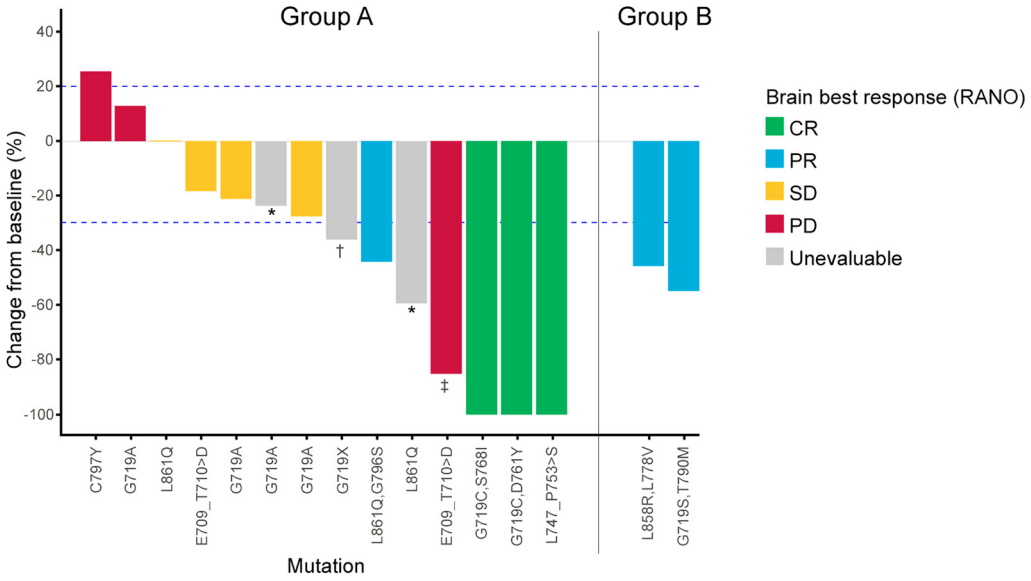

Figure 3. Waterfall plot revealing the maximal response in the size of measurable brain metastases. The corresponding EGFR mutations are depicted below. *Received radiotherapy to brain lesions; †missing data about clinical condition; ‡clinical deterioration. CR, complete response; PD, progressive disease; PR, partial response; SD, stable disease.

Table 3. Mechanisms of Resistance Found at PD on Osimertinib

Patient #	52	10	1	51	54	59	18	16	60	23	9	14	25	27
1∘EGFR mut	R108K	G719X	G719A	L861Q	L861Q, EGFR amp	G719A	L833V H835F	G719A	G719S T790M	L861Q G796S	G719X G709	L861Q	L861Q. L62R	L747_P753delinsS
Novel EGFR mut			E709K			E709K						C979S	D587Y	
TP53 mut														
PIK3CA mut														
cMet amp														
NE														
PFS (mo)	1.2	3.8	5.5	6.7	7.9	8.5	8.8	9	9.3	10.9	13.2	15.7	18.9	24.3

Note: Cases are arranged by length of PFS.
Shaded squares indicate the relevant genetic abberation per patient.
#, number; amp, amplification; mut, mutation; NE, neuroendocrine transformation; PD, progressive disease; PFS, progression-free survival.

assessment of the change in the maximal diameter of the lesions, three had CR (19%), six had PR (38%), six had SD (38%), and one patient had PD (6%); ORR based on radiology only was 56%. Nevertheless, for two patients radiotherapy was given before assessment of response, and for one patient clinical data were missing, not allowing evaluation by RANO-BM. Of the 13 patients with relevant data availability, RANO-BM evaluation identified three patients with CR (23%), three with PR (23%), four with SD (31%), and two with PD (15%); ORR was 46%. One of the patients who had PR by imaging (85% reduction in size of BM, with E709_T710>D mutation) was deteriorating clinically and therefore had PD by RANO criteria. Figure 3 reveals a waterfall plot of the best response of the measurable brain metastases for groups A and B. Of the 40 patients with data available about sites of disease progression on osimertinib, 12 (30%) had brain progression (five—brain alone; seven—brain combined with systemic progression). In groups A and B, 10 (23%) and two (12%) had brain progression (brain alone or combined with systemic), respectively.

Mechanisms of Resistance

For 14 patients, a tissue or liquid biopsy was performed at the time of progression on osimertinib. For 12 of these patients, next-generation sequencing was performed by the investigators, and these data were collected. A variety of methods was used, in all cases allowing detection of mutations and fusions in a large set of cancer-related genes. The results of the pre-osimertinib molecular analysis and the post-progression analyses for these 14 patients are presented in Table 3 and Supplementary Table 2. Potential mechanisms of resistance were identified in seven patients (50%). In four cases, the appearance of an additional EGFR mutation was found, but only one of these was C797S. In three cases, a novel TP53 mutation was identified, and in one case each c-Met amplification and PIK3CA mutations were found. In one case of repeat tissue biopsy, a neuroendocrine carcinoma was found.

Safety

Adverse events (AEs) were in accordance to the recognized toxicities of osimertinib and are summarized in Supplementary Table 3. No grade 5 AEs occurred.

Discussion

We report here the results of the largest cohort to the best of our knowledge of ucEGFRmut treated with osimertinib as the first EGFR TKI. In our cohort of 60 patients, we found an ORR of 61%, an mPFS of 9.5 months, and a median DOR (mDOR) of 17.4 months. Regarding

only patients with no concurrent common mutations or T790M (group A, n = 44), the ORR was 60%, mPFS 8.6 months, and mDOR 11 months. These data are comparable with the only prospective study of osimertinib in ucEGFRmut, the Korean KCSG-LU15-09,[15] with ORR of 50%, mPFS 8.2 months, and mDOR 11.2 months. The PFS was significantly better in patients with compound mutations including a common one, compared with the rest of ucEGFRmuts, whereas TP53 mutations were associated with a trend for worse outcome. We have identified a 46% intracranial response rate to osimertinib (by RANO-BM). In addition, rebiopsy molecular analysis of 12 patients was available, providing a unique set of data regarding the potential mechanisms of resistance in this scenario. Interestingly, novel TP53 was identified in some of these patients and potentially indicates a less recognized mechanism of acquired resistance.

The most prevalent ucEGFRmut is exon 18 G719X, in the EGFR phosphate-binding P-loop. Chiu et al.[18] report 78 of such patients, with an ORR to first-generation EGFR TKIs of 36.8% and 6.3 months mPFS (including both first and later treatment lines). Within the combined analysis of LUX-Lung 3 and 6, along with the phase 2 LUX-Lung 2 trial, 18 patients with G719X mutations treated with afatinib were identified and the corresponding ORR was 78%, with a mPFS of 13.8. Yang et al.[19] report 194 TKI-naive, afatinib-treated G719X patients (from the LUX-Lung studies and additional cohorts), with TTF at 14.2 months and ORR at 61%. Jingran et al.[16] report of four such patients receiving first-line osimertinib, with time on treatment of 5.8 months In our cohort, the ORR to osimertinib within the G719X group excluding those with concomitant common mutations, accounting for 16 patients, was 53%, mDOR 9.1 months, and mPFS 8.6 months. Notably, the LUX-Lung prospective trials included patients who are likely more fit than real-world patients. Nevertheless, detailed structure-function studies predict G719S mutation to shift the P-loop and hinder binding of osimertinib, but to be inhibited by second-generation EGFR TKI poziotinib and potentially also by afatinib.[20] In contrast, another preclinical study revealed higher inhibition of an EGFR G719A model by osimertinib compared with afatinib.[21] Importantly, different G719X mutations (i.e., G719A, C, S or D) had markedly different IC50 to the tested EGFR TKIs. Further data are required to conclude which EGFR TKI is optimal for patients harboring different G719X mutations.

Exon 21 L861Q is the second most common ucEGFRmut. It is located in the activation loop, causing a confirmational change to an active form, and predicted to be affected by various EGFR TKIs relatively similar to the common mutations.[20] In preclinical studies, the L861Q mutation seems to be resistant to first-generation TKIs.[22] A large cohort of patients with NSCLC harboring L861Q mutations has been reported by Chiu et al.[18] Among 54 patients, ORR to TKIs was 40% and mPFS was 8.1 months with the first-generation TKIs erlotinib or gefitinib. As mentioned previously, this report included both patients treated with first and later lines. In the analysis of the LUX-Lung studies, Yang et al.[12] report of 16 patients with L861Q, treated by afatinib on the LUX-Lung trials, with a 56.3% ORR, mPFS of 8.2 months, and mOS of 17.1 months. Yang et al.[19] also report of 109 TKI-naive, afatinib-treated L861Q patients (including 16 from the LUX-Lung trials) with a TTF of 11.5 months and ORR of 58%. Jingran et al.[16] report of 10 patients with this mutation receiving first-line osimertinib, with time on treatment of 19.3 months. Our data from the UNICORN study reveal within the group of patients harboring the L816Q mutations with no common co-mutations, accounting for 11 patients, an ORR of 78%, mDOR of 16 months, and mPFS of 15.7 months, comparing favorably with previous reports.

Nine of the patients recruited within our study harbored a de novo exon 20 T790M mutation. In general, such mutations have greater preclinical sensitivity to osimertinib than to gefitinib, erlotinib, or afatinib, although limited data are available.[23] Yang et al.[12] report of 14 such patients treated with afatinib with an ORR of 14.3%, mDOR of 8.2, and a mPFS of only 2.9 months. The later report of TKI-naïve, afatinib-treated patients included 59 T790M cases with TTF of 4.7 months and ORR of 26%.[19] In our study, the ORR among this subgroup was 44%, mDOR 46.2 months, with mPFS 12.7 months. Two of the nine patients with T790M had a compound with another uncommon mutation (G719X, S768 and T790M and G719S with T790M, both with SD as best response). Notable is the long DOR in the four T790M responders in our cohort.

Interestingly, S768I is often reported as one of the prevalent ucEGFRmuts (36% in a review summarizing five studies; four of which from East Asia), but it was found in only three patients in our cohort (5%).[9] A low proportion of this mutation was also reported in the USA study by Jingran et al.,[16] with only 3.9% of such mutations, in an Italian study (2.9% of ucEGFRmut),[24] and in a recent large German data set,[25] suggesting a difference in the prevalence of this mutation between Asian and Western population. This difference stresses the need of evaluating both western and Asian populations regarding lung cancer in general and specifically EGFR-addicted tumors.

A large proportion of our cohort had compound mutations of a combination of common and uncommon mutations. In general, 45% of our cohort had compound mutations, which is in line with one of the largest reported cohorts of EGFRmut (n = 1023) with 38.6%

compound mutations.[19] Preclinical studies indicate that most compound mutations occur on the same allele (i.e., *cis* arrangement) and reveal in vitro reduced sensitivity to EGFR TKIs when compared with EGFR single common mutation.[23] Regarding group B in our study, of compound common with uncommon mutations subgroup (including also one patient with a single de novo T790M mutation), we found an ORR of 61%, mPFS of 30 months, and mDOR of 46.2 months (Table 2 and Supplementary Fig. 1). These results compare favorably with the results of osimertinib in patients with only common mutations. Our data therefore suggest that compound mutations that include a common mutation can be treated safely with osimertinib, similarly to single common mutations. A recently published large study by the national Network Genomic Medicine in Germany reported a similar observation.[25]

Osimertinib was found to have high CNS penetration and activity.[26] In the AURA trial including almost exclusively patients with common EGFR mutations, CNS ORR in patients with one or more measurable CNS lesions was 70% with a median duration of CNS response of 8.9 months and CNS mPFS of 11.7 months. In our UNICORN study, brain response was available for 13 patients, with a 46% RANO-BM response rate. It should be noted that only two of the six responders by the RANO-BM criteria harbored common mutations (L858R and T790M) as a compound with an uncommon mutation. We conclude that both patients with single ucEGFRmut and with compound uncommon with common mutations can have brain response to osimertinib.

Our study includes 14 patients with a rebiopsy done at the time of progression on osimertinib. Mechanisms of resistance to osimertinib in patients with ucEGFRmut identified in this analysis include acquisition of additional EGFR mutations, novel TP53 mutations, c-Met amplification, PIK3CA mutation, and neuroendocrine transformation. This pattern is generally similar to that found in cases with common EGFR mutations that evolve osimertinib resistance.[3,5] The novel EGFR mutations we identified include C797S (the binding site of osimertinib),[4] E709K, and D587Y. D587Y is in the extracellular EGF binding site and has not been reported so far as a resistance-associated mutation. E709K is located in exon 18, reported to be less sensitive to third-generation EGFR TKIs. TP53 has been reported to associate with poor prognosis when identified at baseline for patients with common EGFR mutations,[20,27] but as a mechanism of acquired resistance, it has been reported only in a single study on the basis of circulating-free DNA.[28] Evolvement of TP53 mutations as a mechanism of acquired resistance to osimertinib requires further studies. No correlation between specific mechanisms of resistance and PFS on osimertinib is apparent from this limited analysis.

The safety profile of osimertinib in this study was acceptable and mostly confined to grade 1 to 2 AEs, which is consistent with previous reports. Osimertinib was associated with a low incidence of discontinuation and dose modification owing to AEs.

Limitations of this study include its observational and retrospective nature. The level of detail in reporting the EGFR mutations was therefore variable. The study was descriptive only; it did not have a formal hypothesis on the effectiveness of EGFR TKIs and was not powered for comparisons between different subgroups. Data regarding resistance mechanisms stem from a small subset of patients who may not be representative of the entire cohort.

In conclusion, the UNICORN study represents the largest set of ucEGFRmut cases treated with osimertinib as the first-line TKI. Most patients were Caucasian, thus substantiating the data mostly coming from East Asian populations.[18] Our results further support the use of first-line osimertinib for patients with ucEGFRmut. The unique assembled database could facilitate treatment choices for patients with uncommon mutations.

CRediT Authorship Contribution Statement

Jair Bar, Alfredo Addeo: Conceptualization, Methodology, Data curation, Writing—original draft preparation, Visualization, Investigation, Resources, Project administration, Supervision, Funding acquisition.

Nir Peled, Sandip Patel, Mirjana Wolner, Ofer Rotem, Nicolas Girard, Frank Aboubakar Nana, Hadas Gantz-Sorotsky, Waleed Kian, Giulio Metro, Yakir Rottenberg, Shiruyeh Schokrpur, Antonio Calles, Mor Moskovitz, Maximilian Hochmair, Alona Zer, Kristof Cuppens, Lynn Decoster, Sofie Derijcke, Martin Reck, Dror Limon, Estelamari Rodriguez, Christoforos Astaras, Adrienne Bettini, Simon Häfliger: Investigation, Resources, Writing—reviewing and editing.

Acknowledgments

No funding was provided to the participating centers. Centralized data collection, statistical analysis, and figure preparation were funded by AstraZeneca. The authors thank Ana Maria Iordan (MD, MSc) and Sorin Tita-Calin for excellent data management, statistical analyses, and figure preparation (MedInteractiv Plus [Bucharest, Romania; funded by AstraZeneca]). The authors also thank Judith Elbaz, Liesbet Lodewyckx, and Nathalie Sassi (AstraZeneca) for helpful discussions.

Supplementary Data

Note: To access the supplementary material accompanying this article, visit the online version of the *Journal of*

Thoracic Oncology at www.jto.org and at https://doi.org/10.1016/j.jtho.2022.10.004.

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