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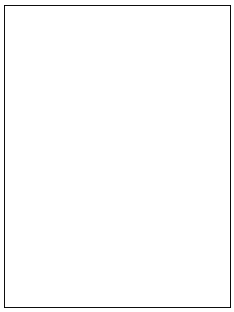

UNcommon EGFR mutations: International Case series on efficacy of osimertinib in Real-life practice in first liNe setting (UNICORN)

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UNcommon EGFR mutations: International Case series on efficacy of osimertinib in Real-life practice in first liNe setting (UNICORN)

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Keywords: NSCLC, metastatic, uncommon EGFR mutation, compound mutations

Abstract

Background

About 10% of EGFR mutations (EGFRmut) are ‘uncommon mutations’ (ucEGFRmut). We aimed to collect real-world data about osimertinib for ucEGFRmut patients.

Methods

This is a multi-center, retrospective study of ucEGFRmut (exon 20 insertions excluded) metastatic NSCLC osimertinib-treated as first EGFR inhibitor. RECIST and RANO-BM brain objective response rate (ORR) were evaluated by investigators. mPFS, mOS and mDOR were calculated from osimertinib initiation. Mutations found at resistance were collected.

Results

60 patients included (22 centres, 9 countries): median age - 64 years, 75% females, 83% Caucasian. The largest subgroups were G719X (30%), L861Q (20%) and *de novo* T790M (15%). ORR was 61%, mPFS 9.5 months (m), mDOR 17.4m, mOS 24.5m. Regarding patients with no concurrent common mutations or T790M (group A, n=44), ORR was 60%, mPFS 8.6 months, mDOR 11 months. For G719X ORR was 47%, mPFS 8.8m and mDOR 9.1m. For L861Q ORR was 80%, mPFS 16m and mDOR 16m. For *de novo* T790M ORR was 44%, mPFS 12.7m, mDOR 46.2m. Compound EGFRmut including common mutations had better outcome compared to only ucEGFRmut. For 13 patients with a RANO-BM evaluable brain metastases, brain ORR was 46%. For 14 patients, rebiopsy was analysed: 4 patients - additional EGFR mutation (C797S, D585Y, E709K), 3 - new TP53 mutation, 1 - c-Met amplification, 1 – PIK3CA mutation and 1 - neuroendocrine transformation.

Conclusions

Osimertinib demonstrated activity in ucEGFRmut with high rate of disease control systemically and intracranially. Several resistance mechanisms were identified. This report comprises, to the best of our knowledge, the largest dataset of its kind.

Introduction

Epidermal growth factor receptor (EGFR[1]) tyrosine kinase inhibitors (TKIs), are considered the standard first-line treatment options for patients with advanced or metastatic non–small-cell lung cancer (NSCLC) harboring sensitizing EGFR mutations[1]. A number of phase III trials demonstrated 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 showed that the 3rd generation TKI, osimertinib, is superior to 1st generation TKIs, erlotinib and gefitinib, in terms of progression free survival (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], as well as for patients positive for T790M resistance mutation after progression on earlier generation EGFR-TKIs[5]. Previous studies highlight 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]. 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 wide-spread 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 (ucEGFRmut) 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 1st- or 2nd generation TKIs in patients with NSCLC ucEGFRmut are inconsistent, based on 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 uncommon EGFR mutations in comparison with those with common sensitizing EGFR mutations (20% *vs.* 76%; 2.2 months *vs.* 11.4 months)[10]. In a different study, Wu et al reported that ORR to 1st generation TKIs, gefitinib or erlotinib was 57.1% in patients with G719X or L861Q mutations, with a mPFS of 6.0 months[11]. A post-hoc analysis on afatinib efficacy from the LUX-Lung 2, LUX-Lung 3, and LUX-Lung 6 trial populations demonstrated an ORR of 71% with a mPFS of 11 months for patients

[1] EGFR: Epidermal growth factor receptor. ucEGFRmut: uncommon *EGFR* mutations TKI: tyrosine kinase inhibitors. RECIST: Response Evaluation Criteria in Solid Tumours. RANO-BM: Response assessment in neuro-oncology brain metastases. WBRT: whole brain radiotherapy. SRS: stereotactic radiosurgery. ORR: objective response rate. mPFS: median progression free survival. TTF: time to treatment failure. mOS: median overall survival. mDOR: median duration of response. Amp: amplification. NE: neuroendocrine. AE: adverse event.

harboring an ucEGFRmut[12] The only outliers were the patients with T790M or exon 20 insertion mutations, who showed a poor ORR and short mPFS (ORR 9-14% and mPFS < 3 months). A larger report including also data from expanded-access programs and phase IIIb studies, identified 315 TKI-naïve, 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%. Based on these findings, the Food and Drug Administration and the European Medicine 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 II study, performed in Korea[15]. Cho and colleagues 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 USA real-world study reported on 20 patients with ucEGFRmut receiving first-line osimertinib[16], with 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, multi-center, real-world retrospective study. Patients included had advanced NSCLC with an uncommon EGFR mutation, 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 part of compound mutations when found together with uncommon mutations. Patients must have received osimertinib as the first EGFR-TKI for their advanced disease. In order 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 centres, 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. Response Evaluation Criteria in Solid Tumours (RECIST) version 1.1 response, as well as Response assessment in neuro-oncology brain metastases (RANO-BM) were evaluated by investigators. Treatment lines administered prior to osimertinib were counted as for advanced disease if completed six months or less prior to the diagnosis of advanced disease. Radiotherapy treatments were categorized as ablative, palliative, whole brain radiotherapy (WBRT) and brain stereotactic radiosurgery (SRS). All data were anonymized prior to their transfer to the lead authors for joint analysis. Data cut-off date was the 17th of September 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 categoric variables. PFS and OS were calculated by Kaplan-Meier method from initiation of osimertinib, duration of response (DOR) was calculated for 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 involved in discussions regarding the study design and collection of the data, but were not involved in discussions about analysis, interpretation of the data, writing of this manuscript and in the decision to publish the results.

Ethics

Each participating centre 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 NIH clinical trials registry (NCT05421936).

RESULTS

Patients:

Data were transferred for joint analysis regarding 65 patients, five of them were excluded (initiation of osimertinib after the cut-off 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 including *de novo* T790M mutation. One additional patient had only *de-novo* T790M mutation. Since 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 of the study cohort, most patients were females with adenocarcinoma, never or past smokers. Seven (12%) patients were initially diagnosed with early disease. Osimertinib was administered as the first-line treatment for advanced disease in 53 (88%) patients; seven patients received prior to osimertinib other treatments for advanced disease: chemotherapy (5 patients, 8%), chemo-immunotherapy (one patient, 2%) or chemo-radiotherapy (2 patients, 3%) treatments. One patient started osimertinib at a dose of 40mg, all others started with 80mg dose. At initiation of osimertinib 23 patients (38%) had brain metastasis. Most patients (51, 85%) had an ECOG-PS of 0-1 at osimertinib initiation. The large majority (50, 83%) were Caucasian. The largest subgroups of included mutations were G719X (18 patients, 30%), L861Q (12 patients, 20%) and *de novo* T790M (9 patients, 15%). Six uncommon variants of exon 19 deletions

were included as uncommon mutations[17] (Supplementary data, Table S1). Compound EGFR mutations were found in 27 patients (45%), TP53 mutations were found in 21 patients (35%). PD-L1 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 RECIST 1.1 was available for 51 patients (85%). Among these 51 patients with evaluable/measurable disease, complete response was reported in four patients (8%; 95% C.I 3-18%, group A – 1 (2%), group B – 3 (23%)), partial response in 27 (53%; 95% C.I 39-66%, group A – 22 (58%), group B – 5 (38%)), stable disease in 16 patients (31%; 95% C.I 20-45%, group A – 11 (29%), group B – 5 (38%)) and progressive disease (PD) in four (8%; 95% C.I 3-18%, all in group A (10%)). ORR was similar between groups A (60%) and B (61%; Table 2). Figure 1A and Figure S1 represents the changes in tumor size and timing of maximal response as well as the details of the mutations. Duration of response is demonstrated qualitatively by the swimmer's plot (Figure 1B). Median time to maximal response in group A was 2.9 months (95% C.I.: 2.7-5.2) and 3.0 months (95% C.I.: 1.9-7.3) in group B.
At data cut-off, 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 – 5, group B – 1). 31 (52%) patients were alive at data cutoff (group A – 21 (48%), group B – 10 (62%)). Median OS was 24.5 months (95% C.I. 17.4-35.1 months). Groups A and B OS was 22.1 months and 31.4 months respectively. An exploratory HR calculated comparing OS of these groups was 0.55 (95% C.I. 0.22-1.36; p=0.19. Figure 2A). Median PFS was 9.5 months (95% C.I 8.5-17.4 months). Groups A and B PFS was 8.6 and 30.0 months respectively (HR=0.24 (95% C.I. 0.09-0.63), p=0.0017. Figure 2B). Median DOR was 17.4 months (95% C.I. 9.1-NA; Figure 2C). DOR for groups A and B was 11.0 and 46.2 respectively (p=0.026; Figure 2C).

Response/PFS/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 evaluable disease. Table 2 demonstrates the response, PFS, OS and DOR by mutation, including G719X, L861Q and *de novo* T790M. Since 21 patients were found to have a TP53 co-mutation, this group was also analyzed separately. Results of groups A and B are reported, as well as the subgroup A of each of G719X and L861Q (i.e., cases that do not harbor concomitant common mutation or *de novo* T790M). DCR was 100% in all of these subgroups besides G719X where one case of PD was seen, as well as in the TP53 subgroup where two cases of PD were reported. ORR was compared for each of the groups to the rest of the cohort and no significant differences were found (data not shown).

In order to further characterize the efficacy of osimertinib in the various mutation sub-groups, each of the mutation sub-groups was compared in terms of PFS and OS to all of

the other patients in the cohort (supplementary Figure S2). None of the comparisons were significant regarding OS. mPFS was longer with a p-value < 0.05 for compound mutations including typical exon 19 deletion or L858R as well as for group B as a whole (in each case comparing to the rest of the study cohort). No corrections for multiple comparisons were done in this exploratory analysis.

Brain efficacy

23 patients (38% of the cohort, 95% C.I. 26-52%; group A – 20 (45%), group B – 3 (20%)) had brain metastasis at presentation. For 16 patients, brain response was evaluable, indicating measurements were available at initiation of osimertinib and at maximal response (Figure 3). Regarding the radiologic assessment of the change in the lesions maximal diameter, 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%. However, for two patients radiotherapy was given prior to 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 (23%) with CR, three (23%) with PR, four (31%) with SD, two (15%) with PD; ORR was 46%. Clinically, one of the patients that 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 demonstrates 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 (5 – brain alone; 7 – brain combined with systemic progression). In group A and B, 10 (23%) and 2 (12%) respectively had brain progression (brain alone or combined with systemic).

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 NGS was performed by the investigators and this data was collected. A variety of methods was utilized, 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 Tables 3 and S2. Potential mechanisms of resistance were identified in seven patients (50%). In four cases the appearance of an additional EGFR mutation was found, only one of these was C797S. In three cases a novel TP53 mutation was identified, in one case each Met amplification and PIK3CA mutations were found. In one case of repeat tissue biopsy a neuroendocrine carcinoma was found.

Safety

Adverse events were in accordance to the recognized toxicities of osimertinib and are summarized in the supplementary table S3. 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% and mPFS of 9.5 months, mDOR 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, mDOR 11 months. This data is comparable to 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. PFS was significantly better in patients with compound mutations including a common one, compared to the rest of ucEGFRmut, while TP53 mutations were associated with a trend for worse outcome. We have identified a 46% intra-cranial 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 were 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 reports of 78 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) [18]. 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 were 78%, with a mPFS of 13.8. Yang et al. report of 194 TKI-naïve afatinib-treated G719X patients (from the LUX-Lung studies and additional cohorts), TTF was 14.2 months, ORR was 61%[19]. Jingran et al report of four such patients receiving first-line osimertinib, with time on treatment of 5.8 months[16] In our cohort the ORR to osimertinib within the G719X group excluding those with concomitant common mutations, accounting for 16 patients, was 53%, median DOR (mDOR) 9.1 months and mPFS 8.6 months. Notably, the LUX-Lung prospective trials included patients that are likely more fit than real-world patients. However, 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 pre-clinical study demonstrated higher inhibition of an EGFR G719A model by osimertinib compared to afatinib.[21]. Importantly, different G719X mutations (i.e. G719A/C/S/D) demonstrated 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 2nd most common ucEGFRmut. It is located in the activation loop, causing a confirmational change to an active form, and predicted to be impacted 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 1st-generation TKIs erlotinib or gefitinib. As mentioned above, this report included both first and later-lines treated patients. In the analysis of the LUX-Lung studies, Yang et al 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[23]. Yang et al. also report of 109 TKI-naïve afatinib-treated L861Q patients (including the 16 from the LUX-lung trials) with a TTF of 11.5 months and ORR of 58%[19]. Jingran et al report of 10 patients with this mutation receiving first-line osimertinib, with time on treatment of 19.3 months[16]. Our data from the UNICORN study demonstrates within the group of patients harboring the L816Q mutations with no common co-mutations, accounting for 11 patients, an ORR of 78%, mDOR 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 gefinitib, erlotinib or afatinib, although limited data are available[24]. Yang et al. 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[23]. 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 were compound with another uncommon mutation (G719X/S768/T790M and G719S/T790M, both with stable disease as best response). Notable is the long DOR in the four T790M responders in our cohort.

Interestingly, S768I is commonly reported as one of the prevalent ucEGFRmut, (36% in a review summarizing five studies; four of which from the far East) but was found in only 3 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)[25] and in a recent large German dataset[26], suggesting a difference in the prevalence of this mutation between Asian and Western population. This difference stresses the need of evaluating both western as well as 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% our cohort had compound mutations, which is in line with one of the largest reported cohorts of EGFRmut patients (n = 1023) with 38.6% compound mutations[19] Pre-clinical studies indicate most compound mutations occur on the same allele (i.e. *cis* arrangement) and demonstrate *in vitro* reduced sensitivity to EGFR-TKIs when compared to EGFR single common mutation[24]. 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, Figure S1). These results compare favorably to 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 on a similar observation[26].

Osimertinib has shown high CNS penetration and activity[27]. 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 was

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 compound with an uncommon mutation. We conclude that both patients with single ucEGFRmut as well as with compound uncommon with common mutations can demonstrate brain response to osimertinib.

Our study includes 14 patients with a re-biopsy done at the time of progression on osimertinib. Mechanisms of resistance to osimertinib in patients with uncommon EGFR mutation identified in this analysis include acquisition of additional EGFR mutations, novel TP53 mutations, c-Met amplification, PIK3CA mutation, as well as neuroendocrine transformation. This pattern is generally similar to that seen 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)[28], E709K and D587Y. D587Y is in the extra-cellular 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 3rd-generation EGFR-TKIs. TP53 has been reported to associate with poor prognosis when identified at baseline for patients with common EGFR mutations[20,29], but as a mechanism of acquired resistance has been reported only in a single study based on circulating free DNA.[30] 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 are 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 due 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.

Conclusions

The Unicorn study represents the largest set of ucEGFRmut cases treated with osimertinib as the first-line TKI. The large majority of 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.

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Figure legends:

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 6 from group B). B. Swimmers' plot of 60 patients, arranged by time on treatment.

Figure 2: Overall survival (OS) (A), Progression free survival (PFS) (B) and duration of response (DoR) (C) of osimertinib-treated patients. Data is 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% C.I. 0.22-1.36; p=0.19), for PFS - HR 0.24 (95% C.I. 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.

Figure 3: Waterfall plot demonstrating 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.

Figure 1A.

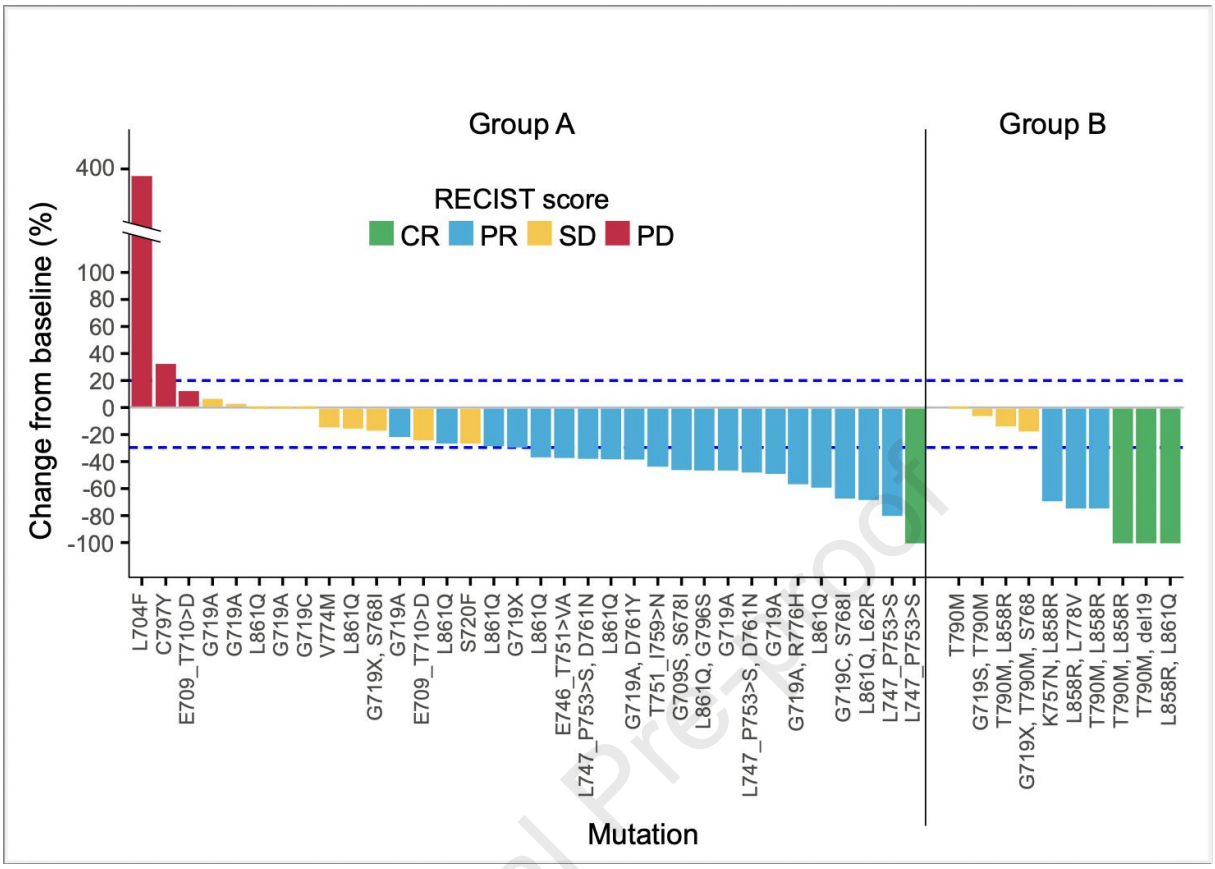


Figure 1B.

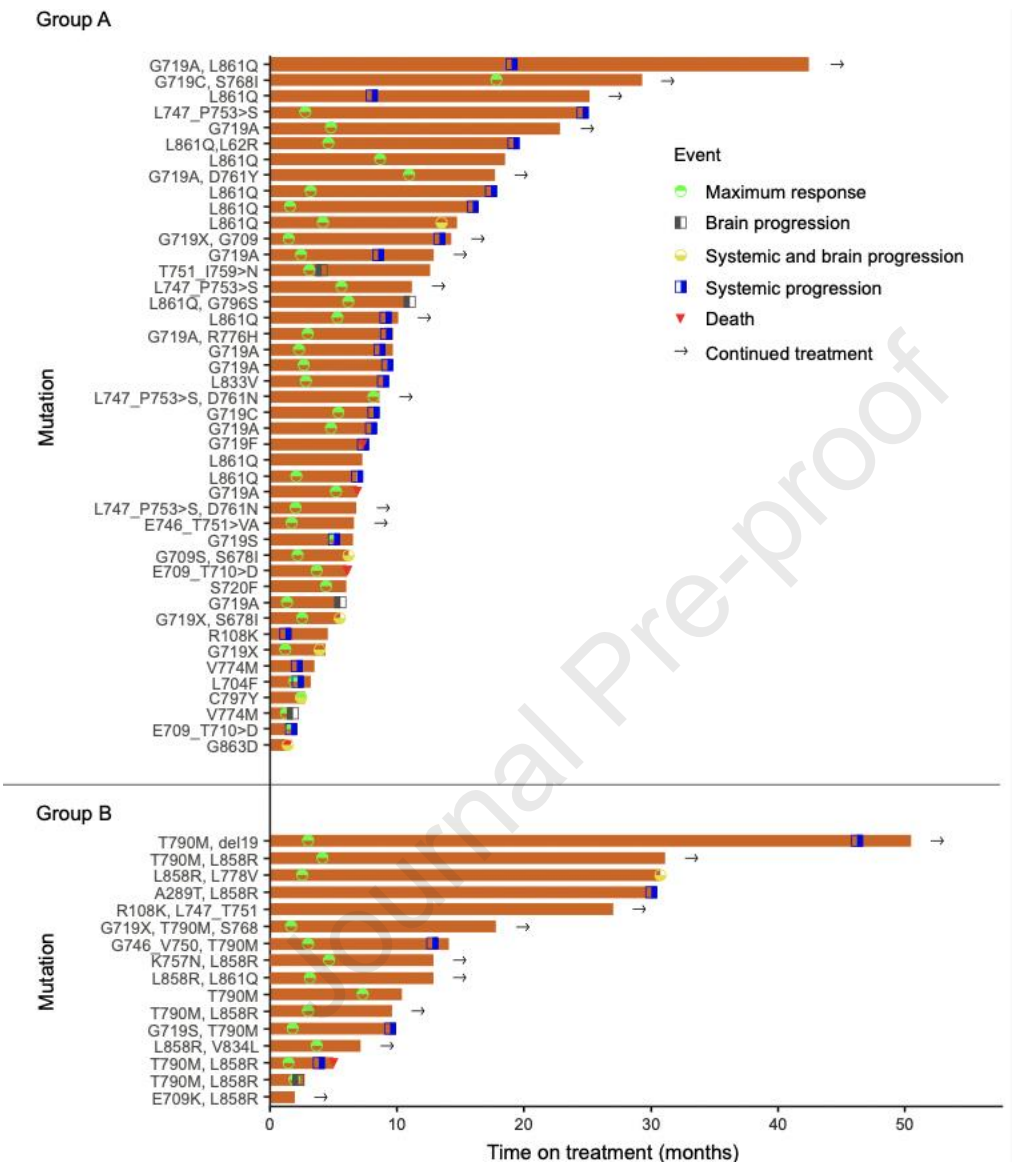
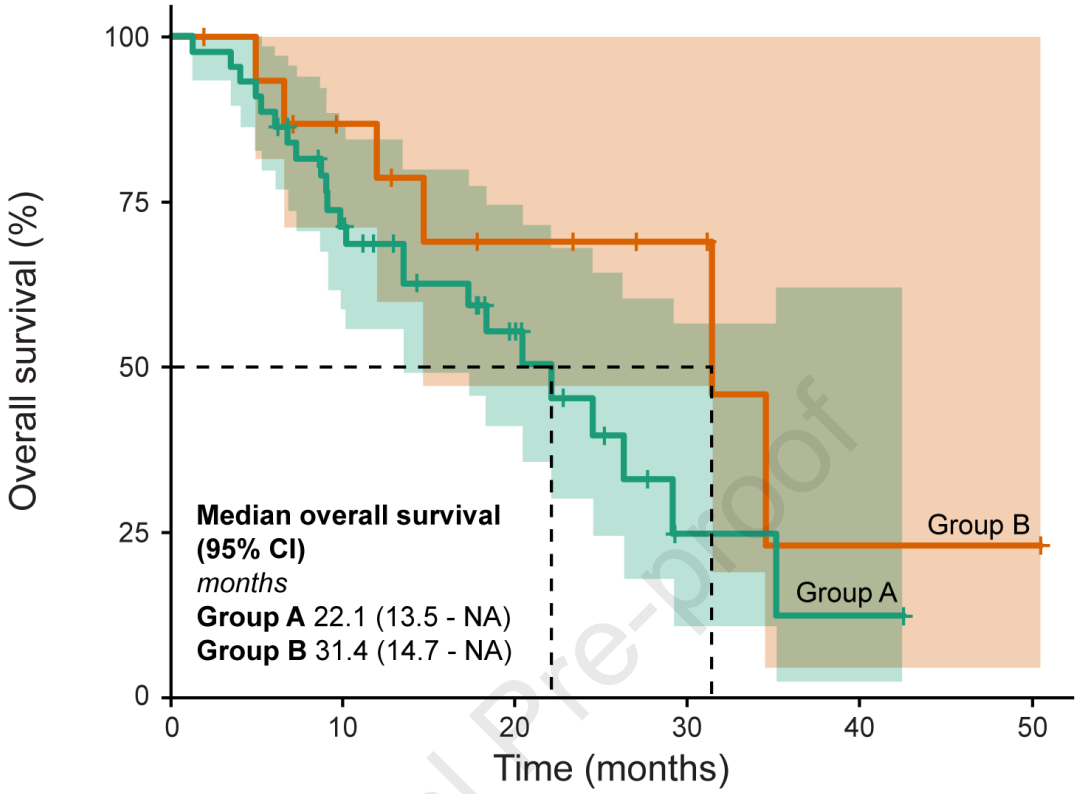


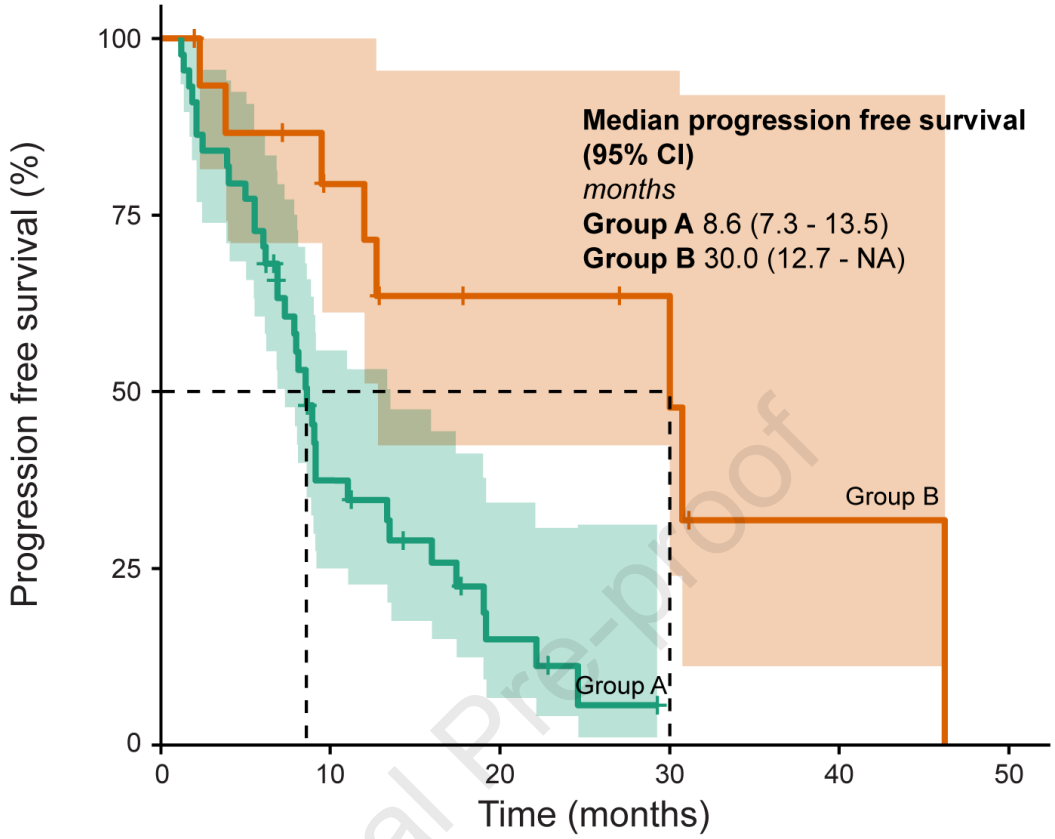
Figure 2A



Number at risk

Group A	44	28	13	2	1	0
Group B	16	11	6	4	1	1

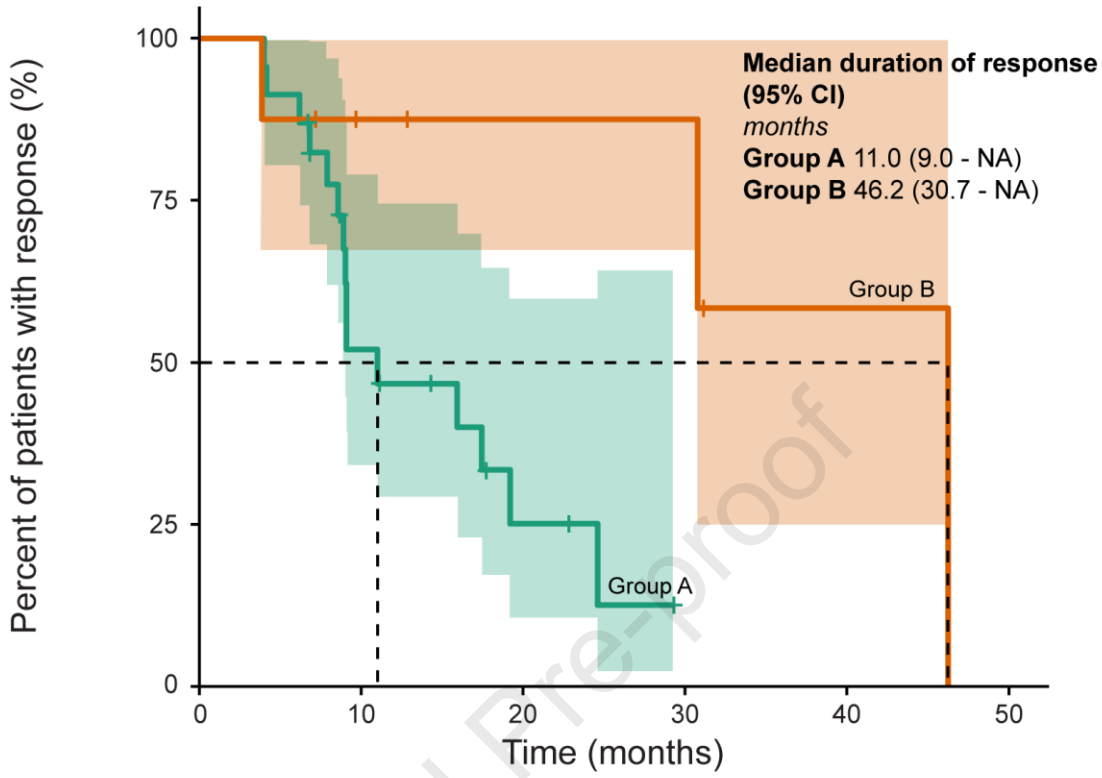
Figure 2B



Number at risk

Group A	44	14	4	0	0	0
Group B	16	10	5	4	1	0

Figure 2C



Number at risk

Group A	23	10	3	0	0	0
Group B	8	5	3	3	1	0

Figure 3

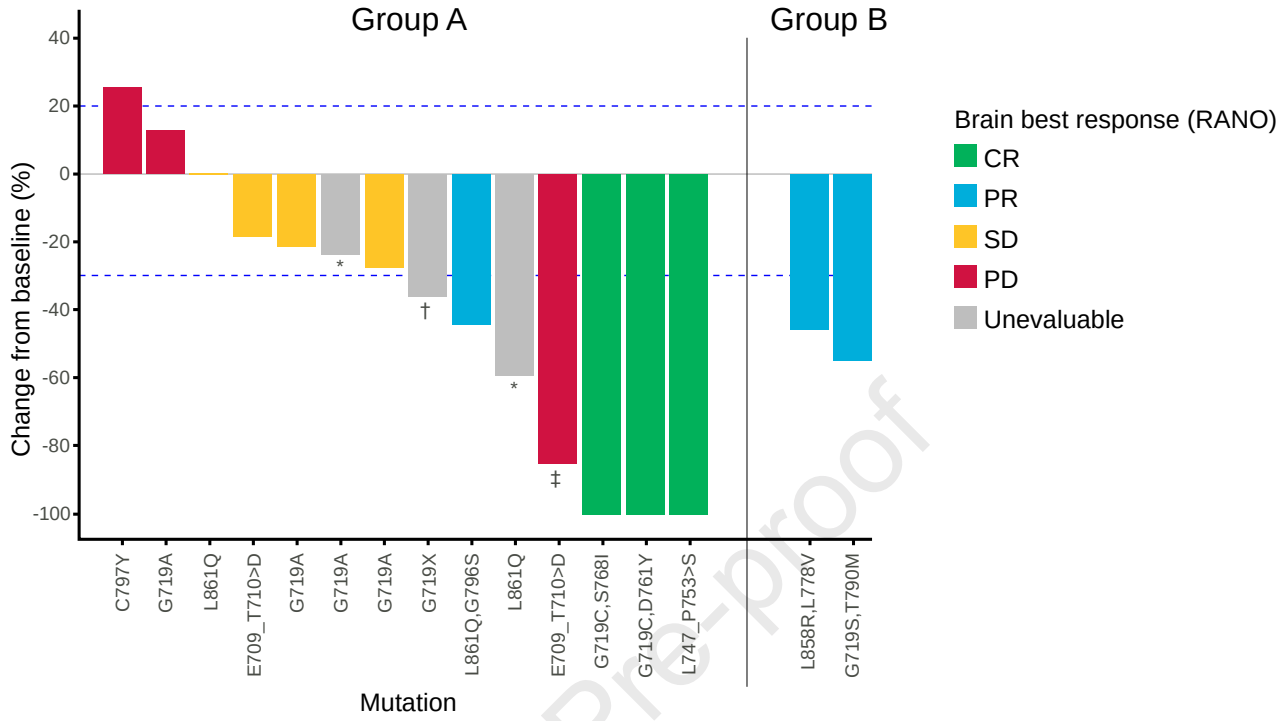


Table 1: patient characteristics.

Characteristics	All study cohort (N=60)	Group A: Uncommon mutations only (N=44)	Group B: Common with uncommon mutations (N=16)
Age (median, range) years	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% C.I. (months)	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*	1 (2)	0	1 (50)
Number of treatment lines for advanced disease prior to 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 prior to osimertinib, n (%)			
Chemotherapy	5 (8)	4 (9)	1 (6)
Chemo-immunotherapy	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)

Characteristics	All study cohort (N=60)	Group A: Uncommon mutations only (N=44)	Group B: Common with uncommon mutations (N=16)
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)
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 cut-off	21 (35)	12 (27)	9 (56)

Percentages were rounded to whole numbers. Due to rounding and patients in more than one category, percentages may not be always 100%. *Durvalumab after chemoradiation. ECOG-PS: eastern oncology group performance status. SRS: stereotactic radiosurgery. WBRT: whole brain radiotherapy. UK: unknown. PD: progressive disease.

Table 2: Efficacy of osimertinib in various subgroups. 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.

	N (% of 60)	RR * (95% C.I.)	PFS Months (95% C.I.)	OS Months (95% C.I.)	DOR Months (95% C.I.)
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/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)

* of patients with evaluable disease. ** common exon 19 deletion mutations (i.e. G746_A750del, L747_T751del).

Table 3: Mechanisms of resistance found at PD on osimertinib

Cases are arranged in by length of PFS.

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						C797S	D587Y	
TP53 mut														
PIK3CA mut														
cMet amp														
NE														
PFS (months)	1.2	3.8	5.5	6.7	7.9	8.5	8.8	9.0	9.3	10.9	13.2	15.7	18.9	24.3

Amp: amplification. NE: neuroendocrine transformation

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