Original Article

Uncommon EGFR mutations in lung carcinoma: features and treatment outcomes in a retrospective French cohort

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Background: The best management for rare epidermal growth factor receptor (EGFR) mutations in advanced non-small cell lung carcinoma (NSCLC) remains uncertain. The literature indicates that response to usual treatment could differ in certain subgroups such as exon 20 insertion/duplication (E20ID), other single uncommon mutation (OSUM), and EGFR complex mutation (ECM).

Methods: In this observational, regional, multi-center, retrospective study, we gathered data on uncommon EGFR mutations in NSCLC from 2007 to 2021. We analyzed patient characteristics, prognostic factors and treatment outcomes [objective response rate (ORR), disease control rate (DCR), progression free survival (PFS) and overall survival (OS)].

Results: Among 119 patients with an uncommon EGFR mutant, 34 harbored E20ID, 23 ECM, and 62 OSUM. There were significantly more non-smokers in E20ID. Female gender and performance status <2 were associated with a better prognosis. Among the 97 metastatic patients with available data for 1st line treatment, median estimated OS was 21 months (95% CI: 18–31 months), with better non-significant OS for ECM. Median estimated PFS was 7 months (95% CI: 4–9 months). We found significant differences in ORR, DCR and PFS favoring 1st line chemotherapy for E20ID, whereas the outcomes for OSUM and ECM were more favorable for tyrosine kinase inhibitor (TKI) (mainly 2nd and 3rd generation).

Conclusions: There were variations in treatment outcomes among subgroups in our cohort. Exon 20 insertions showed better ORR and PFS with 1st line chemotherapy compared to TKI. Conversely, other rare EGFR mutations including ECM had better ORR and PFS with TKI than chemotherapy. There was no significant difference in OS among treatment groups overall or within rare mutation subgroups.

Keywords: Lung cancer; non-small cell lung carcinoma (NSCLC); uncommon epidermal growth factor receptor (EGFR) mutation; rare EGFR mutation

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Introduction

In advanced non-small cell lung carcinoma (NSCLC), epidermal growth factor receptor (EGFR) mutations account for approximately 10% to 15% of NSCLC cases in the non-Asian population and around 40% in the Asian population (1,2). Most EGFR mutations are deletions in exon 19 and L858R, i.e., amino acid substitution Leu858Arg in exon 21. These are referred to as common EGFR mutations and represent 85% to 90% of EGFR mutants (3). Therefore, around 10% harbor an EGFR mutation that is considered uncommon or rare.

The increasing use of next generation sequencing (NGS) has led to more frequent diagnosis of uncommon EGFR mutations. This higher rate of diagnosed mutations has resulted in uncertainty regarding the best treatment option(s) for each mutation. Up until 2017, only a limited number of mutations were investigated, mainly through polymerase chain reaction and Sanger sequencing. Those mutations were most frequently E709X and G719S in exon 18, in phase deletion in exon 19, insertions, T790M and S768I in exon 20 and L858R and L861Q in exon 21. Afterwards, NGS led to more extensive sequencing and the detection of more types of mutations (4). The treatment of metastatic NSCLC has been well documented for common mutations, particularly treatment using tyrosine kinase inhibitors (TKIs). The gold standard treatment for advanced NSCLC with common mutations is third generation TKIs like osimertinib, which have proven to provide better progression free survival (PFS) and overall survival (OS), with a safety profile similar to first generation TKIs (5). Current debate still remains over simultaneous use of TKI and VEGF antibodies, simultaneous use of chemotherapy and TKI with associated toxicity, and the role of immunotherapy (6-8) FLAURA 2 study.

The best management for rare mutations in NSCLC remains uncertain and is based on post hoc and/or case study analysis. For instance, FDA approval of 2nd generation TKI afatinib to treat some rare EGFR mutations (S768Q, L861Q, G719X) used a post hoc analysis of LUX Lung 2, 3 & 6 studies, which had a total of 32 pooled patients (9).

Literature on rare EGFR mutations in lung carcinomas underlines the need to split rare EGFR mutations into subgroups that may respond differently to treatment. These subgroups include: (I) exon 20 insertion/duplication (E20ID), (II) EGFR complex mutations (ECM), which are either a combination of two rare EGFR mutations or mixed rare EGFR mutation with one common EGFR mutation, and (III) other single uncommon mutations (OSUM).

Recent literature shows that OS for OSUM patients may be better with chemotherapy than TKIs, with exceptions including ECM (10). There are also developments of new TKIs for E20ID, including poziotinib, mobocertinib, which are still under phase 2 or 3 study in 2021 (11). Additionally, E20ID could benefit from the synergistic EGFR-MET antibody amivantamab, and TKI is still under trial (12). In the USA, the FDA has approved a license for amivantamab and mobocertinib for E20ID, but only as 2nd line treatment for now.

Our cohort takes another step towards better understanding rare EGFR mutations in lung carcinomas. Here, we provide one of the largest uncommon EGFR mutant multicentric cohorts with both exon 20 and other uncommon mutants, and we report on comprehensive patient characteristics and treatment outcomes. We present the following article in accordance with the STROBE reporting checklist (available at https://jtd.amegroups.com/article/view/10.21037/jtd-21-1924/rc).

Methods

In this retrospective, regional study, patients were selected from the anatomic pathology databases of the Regional Oncology Center (CGFL, Dijon, France) and the Dijon-Burgundy University Hospital (CHU Dijon-Bourgogne, France). We collected available data on patient characteristics and tumor management from whichever French facility was in charge of patient treatment. This implied reviewing patient files from 12 different hospitals.

This study was conducted in accordance with the Declaration of Helsinki (as revised in 2013) and Guidelines of the International Conference on Harmonization. It was approved by the institutional ethics committee of the Cancer Center GF Leclerc and living patients were informed and had the opportunity to decline study participation.

Inclusion criteria were: patients over 18 years with lung cancer diagnosis of any stage, with a rare EGFR mutation identified at the CGFL or CHU Dijon from 1 January 2007 to 15 January 2021. We excluded patients with common EGFR mutations (exon 19 deletion and L858R) as well as secondary T790M mutations associated with an original common EGFR mutation for which the treatment strategy is well documented.

For the EGFR analyses, DNA was isolated from tumor

tissue samples using the Maxwell16 FFPE Plus LEV DNA Purification kit (Promega, Madison, WI, USA). The quantity of extracted genomic DNA was assessed by a fluorimetric method with a Qubit device. From 2007 to 2016, hotspot mutations in the EGFR gene were detected by allelic discrimination, fragment analysis and Sanger sequencing. From 2017, all coding exons of the EGFR gene (exons 18 to 21) were analyzed by NGS. Four hundred ng of genomic DNA were used for library preparation using the Agilent Sure Select XT reagent kit (AgilentTechnologies, Santa Clara, CA, USA). The entire enriched library was used in the hybridization and captured with Sure Select custom designed baits (Agilent Technologies). Following hybridization, the captured libraries were purified according to the manufacturer's recommendations. Normalized libraries were pooled and DNA was sequenced on an Illumina MiSeq (Illumina) device using 2*111-bp paired-end reads.

Data was collected for patient characteristics, tumor characteristics and treatment. Patient characteristics included date of birth, sex, smoking status, body mass index (BMI), occupational exposure, cardiovascular and respiratory comorbidities, performance status at stage IV diagnosis, last follow-up or date of death. Tumor characteristics included date of lung cancer diagnosis, date of rare mutation diagnosis, date of stage IV diagnosis, histology, programmed cell death 1 ligand 1 (PD-L1) status, tumor localization, EGFR mutation(s), and allelic frequency if available. Finally, treatment data concerned prior treatment of stage IV and rare EGFR mutation diagnosis if any. Moreover, for each line of treatment after stage IV diagnosis, we collected date of treatment introduction, date of progression, date of ending and finally best objective response on computed tomography (CT) imaging when available.

Patient and tumor characteristics were described regardless of the disease stage at diagnosis. As for treatment options and outcomes, analyses were performed only in metastatic patients with available data for the 1st line of treatment. Data was presented overall and for the 3 subgroups: E20ID, ECM and OSUM.

We analyzed patient characteristics and treatment outcomes in terms of response rate, PFS and OS. OS was defined as time between the diagnosis of an uncommon mutation in EGFR during metastatic disease and death from any cause. PFS was defined as the time between treatment onset and progression or death. Objective response rate (ORR) was defined as the sum of complete and partial response rate on CT. Disease control rate (DCR) was defined as the sum of complete, partial and stable response.

Statistical analysis

Comparisons of tumor and patient characteristics according to the type of mutation were performed using Chi2, Fisher or Student tests, as appropriate. Median follow-up was obtained with a reverse Kaplan-Meier estimate. Survival analyses were performed using the Kaplan-Meier method, and comparisons between groups used the log rank test. As ECM is sometimes reported in previous literature (10,13) as having a better prognosis, the OS of this subgroup was also compared to pooled OSUM and E20ID. Prognostic factors for OS were determined with a Cox model and using backward stepwise selection of variables including gender, ever-smoker, obesity, professional exposure, cardiovascular comorbidity, performance status and tumor PD-L1 status.

Sub-analyses were carried out on two highly represented uncommon mutations: L861Q and G719X.

P value less than 5% was considered as significant. All tests were two-sided. Statistical analyses were performed using R v4.0.5 software.

Results

Patient and tumor characteristics

Of the estimated 9,520 NSCLC samples screened, we identified 164 samples with lung cancer and an uncommon EGFR mutation. After the withdrawal of duplicates (i.e., patients diagnosed twice) and screening errors, 119 patients with available medical records were reviewed. Out of those 119 patients, 97 had metastatic disease with at least one documented 1st line of treatment (see *Figure 1*).

The annual number of diagnosed uncommon EGFR mutations more than doubled from 2016 to 2017, and then dropped back considerably in 2020 (Figure S1). Among the 119 rare mutations analyzed, 34 were single E20ID, 62 were OSUM, and 23 were ECM. The main mutations among OSUM were G179X and L861Q (*Figure 2*). Among 23 complex mutations, 14 were composed only of rare EGFR mutations and 9 of mixed uncommon/common mutations (5 L858R and 4 T790M). Among the 14 complex mutations harboring only rare mutations, S768I was found in 7 cases; G719X in 7 cases; and L861Q in 6 cases.

In this cohort, 93.3% were adenocarcinoma cases, 4 of which had a bronchioloalveolar presentation, and 3.3%

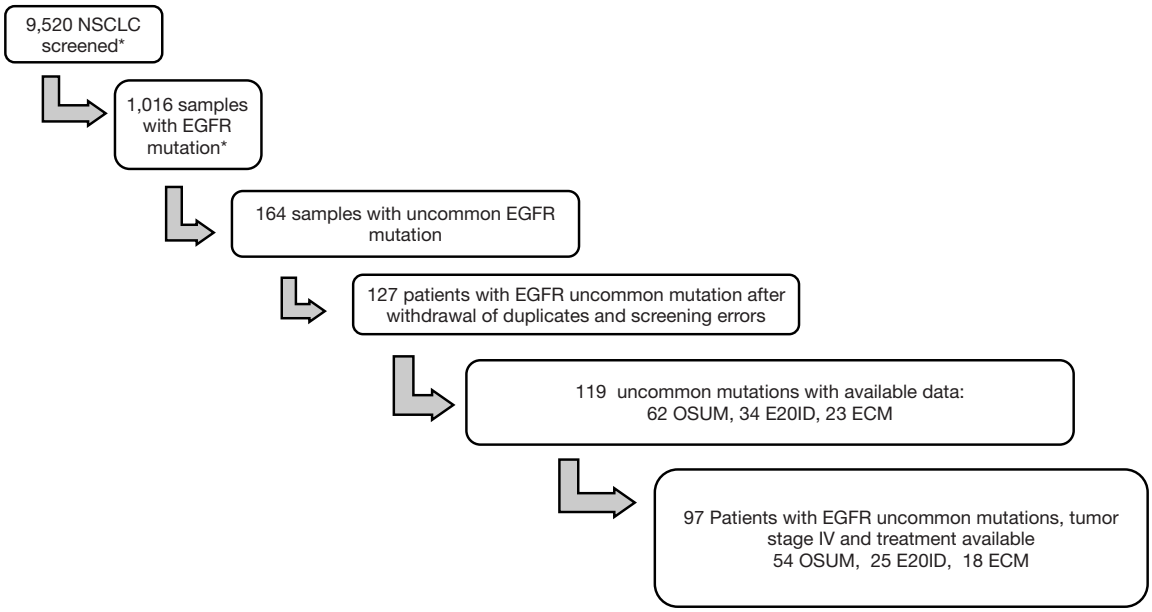

Figure 1 Flow chart of the French regional retrospective cohort. *, due to the 2 databases and the impossibility to unit withdrawal of duplicates apart from individual file review these 2 figures are estimated. NSCLC, non-small cell lung carcinoma; EGFR, epidermal growth factor receptor; OSUM, other single uncommon mutation; E20ID, exon 20 insertion/duplication; ECM, EGFR complex mutation.

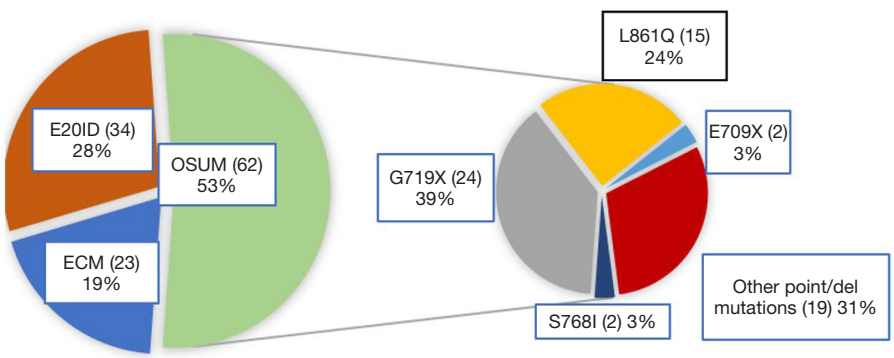

Figure 2 Distribution of rare EGFR mutations in the 119 patients analyzed. E20ID, exon 20 insertion/duplication; ECM, EGFR complex mutation; OSUM, other single uncommon mutation; EGFR, epidermal growth factor receptor.

were squamous cell carcinoma. When known, PD-L1 status was null in 44.6%, (1–50%) in 36.4%, and >50% in 19%. There were no significant differences in tumor characteristics in E20ID *vs.* OSUM and ECM (*Table 1*). In this cohort, 78.2% had a metastatic location at diagnosis: 26.8% cerebral, 61.3% pulmonary or pleural, 44.1% bone, 14% adrenal and 16.1% liver.

The patients in this cohort were 57% women, and mean age at diagnosis was 67 years. Overall 39.7% were never-smokers, but the rate was much higher in the E20ID group (58.8%) compared to ECM & OSUM (31.7%). Smoking status was the only significantly different characteristic between the two subgroups (*Table 1*). Other patient characteristics included a mean BMI of 25.1 and professional exposure in 13%, mainly asbestos. Finally, performance status at diagnosis was mainly 0–1 (72.6% *vs.* 27.4% for 2 or 3).

Almost 37% of the 119 patients were still alive at last

Table 1 Main tumor and patients characteristics

Characteristics	Overall (n=119)	E20ID (n=34)	OSUM (n=62)	ECM (n=23)	P value
Main patient characteristics					
Sex[a]					0.86
Female	68 (57.0%)	20 (58.8%)	36 (58.1%)	12 (52.2%)	
Age, years, mean [SD]	67 [10]	70 [10]	66 [11]	66 [9]	
Smoking status (3 missing values)[a]					0.004
Non-smoker	46 (39.7%)	20 (58.8%)	18 (30.0%)	8 (36.4%)	
Current smoker	27 (23.3%)	2 (5.8%)	19 (30.7%)	6 (26.1%)	
Former smoker	43 (37.0%)	12 (35.3%)	23 (37.1%)	8 (34.8%)	
BMI at diagnosis (20 missing values)[b]					0.48
Mean	25.1	26.6	24.6	24.3	
Professional exposure (26 missing values)[a]					0.40
Yes	12 (13.0%)	5 (14.7%)	6 (16.2%)	1 (4.0%)	
Performance status if known (13 missing data)[a]					0.41
0–1	77 (72.6%)	24 (70.6%)	34 (54.8%)	19 (82.7%)	
2	21 (19.8%)	7 (20.6%)	9 (14.5%)	5 (21.7%)	
3	8 (7.6%)	1 (2.9%)	7 (11.3%)	0	
Main tumor characteristics					
Histology[a]					0.92
Adenocarcinoma	111 (93.3%)	33 (97.1%)	58 (93.6%)	20 (87.0%)	
Other	8 (6.7%)	1 (2.9%)	6 (9.7%)	1 (4.3%)	
PD-L1 status (% on data available) [45 (38%) missing values][c]					0.86
PD-L1 negative	33 (44.6%)	11 (45.8%)	15 (35.0%)	7 (41.0%)	
PD-L1 positive	41 (55.4%)	13 (54.2%)	21 (49.0%)	7 (41.0%)	
PD-L1 >50%	14 (19.0%)	4 (16.0%)	7 (16.0%)	3 (18.0%)	
Known initial metastasis [2 (1.6%) missing values][a]					
Yes	93 (78.2%)	27 (79.4%)	51 (82.0%)	15 (71.0%)	0.66
Cerebral location	25 (26.8%)	7 (25.9%)	17 (27.0%)	1 (4.0%)	0.07

[a], Ki2 Pearson; [b], F test; [c], Ki2 Pearson on positivity. E20ID, exon 20 insertion/duplication; OSUM, other single uncommon mutation; ECM, EGFR complex mutation; BMI, body mass index; PD-L1, programmed cell death 1 ligand 1.

follow-up <6 months, 52% were deceased, and 11% were lost to follow-up. The mean follow-up time was 21 months (Table S1).

Out of the 97 metastatic patients with a 1st line of treatment, 25 were single E20ID, 54 were single OSUM, and 18 were ECM, among which 9 were common/uncommon combination and 9 were only composed of uncommon mutations (of which only one had E20ID mutation) (Figure S2).

Treatment options and respective outcomes for metastatic patients

The two main 1st line treatments in our 97 patients were chemotherapy (29%) and TKI (54%). Other treatments included palliative care for 9 (9.2%), immunotherapy for 5 (5.2%) and 1 radiotherapy as well as 1 surgical treatment for an isolated secondary metastasis.

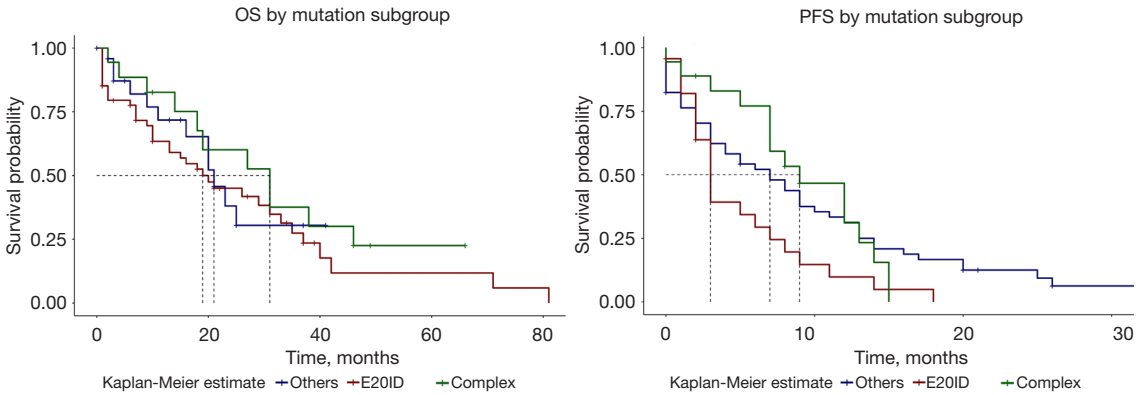

Figure 3 OS and PFS by mutation subgroups. E20ID, exon 20 insertion/duplication; OS, overall survival; PFS, progression-free survival.

The 1st line treatment administered to E20ID was mainly chemotherapy, whereas most OSUM and ECM patients received TKI. TKI were mostly 2nd or 3rd generation (afatinib 51%, gefitinib 21%, erlotinib 15%, osimertinib 6%). Chemotherapy was mainly platinum doublets (>85%), with some cases of monotherapy (Table S2).

A 2nd line treatment was given in around half of the 1st line treatment population, and about a quarter received a 3rd line treatment; 2nd line treatment was 48% (24 patients) chemotherapy; 19 of them had previously received TKI. TKI was the 2nd line treatment in 32% (16 patients), of whom 8 had already had TKI as 1st line; 14% of 2nd line therapy was immunotherapy.

The ORR was 45.4% in the overall population, 46.3% in OSUM, and 36% in E20ID. Regarding 1st line treatment with TKI, the OSUM group had an ORR of 63.6% compared to 20% for the E20ID group. The trend was the contrary for chemotherapy, with 25% ORR *vs.* 53.8%, respectively (Table S3). The difference in ORR was significant (P<0.002). There was a similar trend for DCR (Table S4). The ORR and DCR were better in the ECM group than for both E20ID and OSUM; 15 out of 18 were treated with TKI at first; two had complete response and six had partial response. Three patients were treated with chemotherapy and all three had partial response.

Overall median PFS was 7 months (95% CI: 4–9 months) (Figure S3). By mutation subgroup, median PFS was 3 months (95% CI: 3–9 months) for E20ID; 7 months (95% CI: 4–12) for OSUM; and 9 months for ECM [95% CI: 7–not available (NA)]; P=0.06 (*Figure 3*). By treatment group, PFS for all uncommon mutations showed a median PFS of 9 months for patients treated with TKI (95% CI: 7–13); 5 months for chemotherapy (95% CI: 3–9); and 1.5 months for palliative care (95% CI: 0–NA); P=0.002 (Figure S4).

When comparing PFS for the two main treatments (chemotherapy *vs.* TKI) and by mutation subgroup, the trend is similar to those for ORR and DCR, with better and significant results for TKI in OSUM and better results for chemotherapy in E20ID (*Figure 4*). Indeed, median PFS in OSUM was 10 months for patients receiving TKI (95% CI: 8–14) and 3 months for those receiving chemotherapy (95% CI: 2–NA) with P=0.04, TKI hazard ratio (HR) =0.46 (0.21–0.99; P=0.05). In E20ID, median PFS was 7 months for chemotherapy (95% CI: 3–NA) and 2 months for TKI (95% CI: 1–NA), P=0.002, HR =6.03 (1.4–25.6; P=0.01). In ECM, median PFS was 12 months for TKI (95% CI: 7–NA). In this subgroup, statistical comparison or estimates were not relevant since there were only 3 complex mutations treated with chemotherapy as a 1st line treatment.

OS of metastatic patients

Median OS was 21 months (95% CI: 18–31) in the overall population (Figure S5).

By mutation subgroup, there were non-significant trends when the 3 groups were analyzed separately, with median OS of 31 months for the ECM group, 22 months for E20ID, and 19 months for OSUM (*Figure 4*). Despite very suggestive survival curves, median OS for the ECM group was also non-significantly greater than pooled E20ID-OSUM (P=0.3; HR =0.7; 95% CI: 0.34–1.34) (Figure S6).

Appendix 1 shows non-significant differences in OS by 1st line treatment in the whole population and in each uncommon mutation subgroup.

OS analysis therefore showed non-significant differences

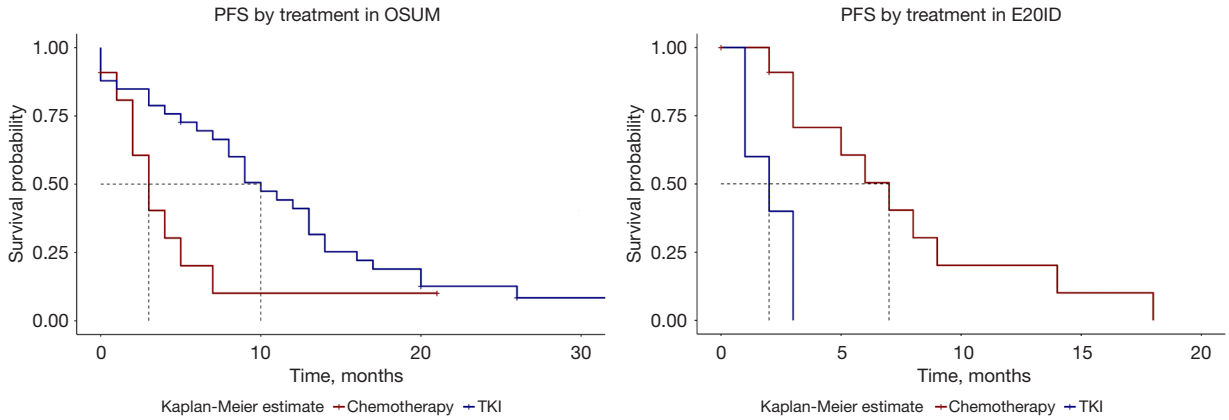

Figure 4 PFS by treatment in OSUM and E20ID. PFS, progression-free survival; OSUM, other single uncommon mutation; TKI, tyrosine kinase inhibitor; E20ID, exon 20 insertion/duplication.

among subgroups of 1st line treatment in all rare EGFR mutations as well as by mutation subgroup. The results remained non-significant for all lines of treatment.

Other analyses

Prognostic factors for OS. Adjusted analysis showed two significant positive prognostic factors: female gender (HR =1.3; 95% CI: 1.1–3.4; P=0.026), and performance status 0, 1 or 2 (median OS: 31 months, 95% CI: 26–42 *vs.* 7 months, 95% CI: 2–18). Other explanatory variables were finally not significant (see Appendix 2). Above average allelic frequency was not associated with better OS or PFS response to TKI in our data.

L861Q and G719X mutations. Even though the result was not significant, L861Q-positive status in our cohort tended to be associated with better PFS and OS than other uncommon EGFR mutations. The opposite was true for G719X status (see Appendix 3).

In patients treated with immunotherapy, our limited results are presented in Appendix 4.

Finally in our data there was no significant differences in OS, FPS or ORR according to the type of TKI used as a 1st line treatment.

Discussion

On the one hand, the patient and tumor characteristics in our cohort are consistent with previous literature.

Considering the year of diagnosis, the large increase that began in 2017 can be linked to the increase in the use of NGS in France as abroad (4). As for 2020, the remarkable decrease is probably due to an increase in deferred diagnoses during the COVID-19 pandemic (14).

The distribution of rare mutations is roughly consistent with those described in previous literature, but with slightly higher proportions of E20ID and G719X (15). This is maybe due to the modest size of our cohort even though it can still be considered substantial for uncommon EGFR mutations. Histology in our cohort is in line with French nationwide EGFR profiling which indicates that 84% of all EGFR mutant NSCLC are adenocarcinomas (16). It should be noted that there was one case of sarcomatoid carcinoma, which is one of the very few cases reported so far for uncommon EGFR mutations (17).

In our cohort of rare EGFR mutants, the non-smoker proportion is higher than the 20% reported in EGFR non-mutant NSCLC. It is similar to the reported 60% of non-smokers in EGFR common mutants in our E20ID subgroup, whereas our OSUM & ECM subgroups had intermediate non-smoker proportions (16). Previous literature showed heterogeneous data, some reporting that E20ID was more frequent in smokers, and other cohorts like ours reporting a majority of never-smokers (3,13). Other characteristics are similar to previous reports showing a majority of women with rare EGFR mutants, with a mean age in the mid-sixties (10,18). Occupational exposure has rarely been studied and reported in uncommon EGFR mutants, but our results were very similar to the 12% to 14% exposure reported in NSCLC worldwide and in France (19,20).

On the other hand, treatment options and respective outcomes are somewhat different than previously reported.

Similar to prior work, our cohort illustrates the absence of strong consensus for the 1st line treatment of choice for

these rare mutations (10).

Our results suggest that there is no significant difference in OS when comparing OSUM, E20ID and ECM. However ECM had non-significantly better OS, as previously reported, particularly when patients were treated with 2nd generation TKI. However, there is still a high level of heterogeneity among complex mutations and their respective outcomes (10,21,22).

We found no significant differences in OS in 1st line treatment subgroups among OSUM, E20ID and ECM. However our data strongly suggests better PFS, ORR and DCR with 1st line TKI in OSUM, and with 1st line chemotherapy in E20ID. These results are consistent with results from a Chinese cohort showing similar trends in OS and PFS (23). Our data also reinforce and complete the existing results for ORR and DCR. Slight differences in the results might be linked to sampling bias as well as numerous differences in study design, including the inclusion of T790M mutation, only 1st generation TKI treatment, no distinction between OSUM and E20ID in the chemotherapy subgroup, and an Asian population with different characteristics.

Concerning OSUM, our results for OS are consistent with a recent similar French study (10). However, their results suggest significantly better OS after a 1st line of chemotherapy compared to TKI, but TKI treatment in this study were almost exclusively 1st generation (10). Our better result with a majority of 2nd and 3rd generation TKI for OSUM is also consistent with a recent international meta-analysis and another recent Japanese analysis suggesting better efficacy of 2nd generation TKI over 1st generation TKI (24,25). In addition, the previous French study did not mention other treatment outcomes such as PFS, ORR or DCR. Our results for PFS in OSUM patients follow the same trends reported in another study, though they reported a greater difference in PFS in favor of TKI (26). Considering our observation that OSUM had better PFS-ORR-DCR for TKI but non-significantly better OS for chemotherapy, we could hypothesize that there might be a mechanism of resistance to TKI that is not yet elucidated. This could lead to initial favorable outcomes followed by more aggressive tumor behavior, or late diagnosis and management of tumor progression.

For E20ID patients in our cohort, the median OS of 22 months is in line with a recent French cohort in which OS was 24 months; PFS was also similar at 7 months, and 70% of the E20ID group was treated with chemotherapy (27). This reinforces preclinical and clinical data in favor of the resistance of E20ID to most available TKI (15,28,29). Exceptions have however been reported for insertions which are not in the so-called loop but within the alpha-C-helix, which could explain some reports on TKI efficacy (15,30). It has also been recently suggested that E20ID could have better OS and PFS with chemotherapy than non-mutant adenocarcinoma (31).

For ECM, we were unable to perform statistical tests due to our small sample size. However, our results suggest no major difference in ORR between 1st line TKI and chemotherapy for complex mutations.

Immunotherapy in uncommon EGFR mutant NSCLC is an active field of research and its place is not univoc (15). Some reports suggests that the tumor micro-environment, which is not responsive to immunotherapy in patients with mutant EGFR, could be modified for instance with anti-angiogenic therapy (32). Still, immunotherapy outcomes could be better in uncommon EGFR mutations than in common ones (33). Our data do not reveal a significant trend due to the small number of patients and the almost exclusive use of immunotherapy, either compassionate use or simultaneous to radiotherapy.

Compared to other studies reporting on common EGFR mutations, the 21 months of OS for all uncommon mutations is close to the 22.6 months reported in patients with a common EGFR mutation, but other studies report OS as high as 35 months (3,27). Our PFS results also suggest that E20ID treated with chemotherapy and OSUM treated with TKI have outcomes similar to common EGFR mutations (3). More specifically, PFS of 10 months for OSUM treated with TKI can be compared to 11.1 months reported in common EGFR mutations, and 7 months for E20ID treated with chemotherapy is similar to 6.5 months in common EGFR mutations.

Finally, observations from the focus on L861Q and G719X patients. While not significant, L861Q positive status in our cohort tended to be associated with better PFS and OS than other uncommon EGFR mutations. These results are consistent with two previous reports but differ from another French cohort in which this variant had a rather poor prognosis when treated with 1st generation TKI (9,10,24). These data tend to confirm the resistance of L861Q to 1st generation TKI, and suggest the use of 2nd or 3rd generation TKI treatment rather than chemotherapy (15,34). On the contrary, patients with the G719X mutant tended to be associated with lower PFS and OS than other OSUM and ECM, even though the results were not significant. To sum up, the better than average OS and

PFS in L861Q and lower than average in G719X is similar to what has been observed previously even though the literature remains heterogeneous (1,35).

Our multicenter study is one of the largest to focus on uncommon EGFR mutations. It is also one of few studies which have considered all rare mutations and then specifically analyzed ECM, E20ID and OSUM categories with pooled and separate analyses. It is also one of the very few of this size in which the TKI treatment were mainly 2nd and 3rd generation, which are now the most commonly prescribed TKI. However, our study has several limitations which are mainly due to its retrospective nature. It implies lack of randomization and numerous information as well as selection biases. In addition, most of our analysis was performed for the ECM, E20ID and OSUM subgroups, which contributes to general orientation on 1st line treatment, but those subgroups are still heterogeneous. Thus, a systematic literature review should be undertaken before making individual treatment decisions when available for the specific mutation diagnosed. Finally, our quantitative outcomes do not include assessment of quality of life under treatment, which has to be taken into account.

Conclusions

Our cohort illustrates the heterogeneity in patient characteristics, prognosis and treatment outcomes among NSCLC patients with uncommon EGFR mutants. Overall treatment outcomes in our cohort were better than reported for wild type patients, but not as good as in patients with common EGFR mutations.

Our data emphasizes differences between subgroups of patients with uncommon EGFR mutations. Those with exon 20 insertions had better ORR and PFS with chemotherapy, which, aside from ongoing trials, seems to be the best current treatment option for most. Other single uncommon EGFR mutation including complex mutation show better results with TKI, which should thus be considered as the 1st line treatment option.

There was no significant difference in OS among 1st line treatment or rare mutation subgroups. This adds valuable complementary information about uncommon EGFR mutations treated with TKIs—mostly 2nd and 3rd generation—to recent work suggesting that OS is better with chemotherapy than 1st generation TKI in uncommon EGFR mutations (E20ID excluded). This investigation provides data which could contribute to decisions about 1st line treatments in patients with uncommon EGFR mutants. However, it does not replace the need for a systematic literature review for specific mutations, which remains heterogeneous even among the described subgroups.

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Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. This study was conducted in accordance with the Declaration of Helsinki (as revised in 2013) and Guidelines of the International Conference on Harmonization. It was approved by the institutional ethics committee of the Cancer Center GF Leclerc and living patients were informed and had the opportunity to decline study participation.

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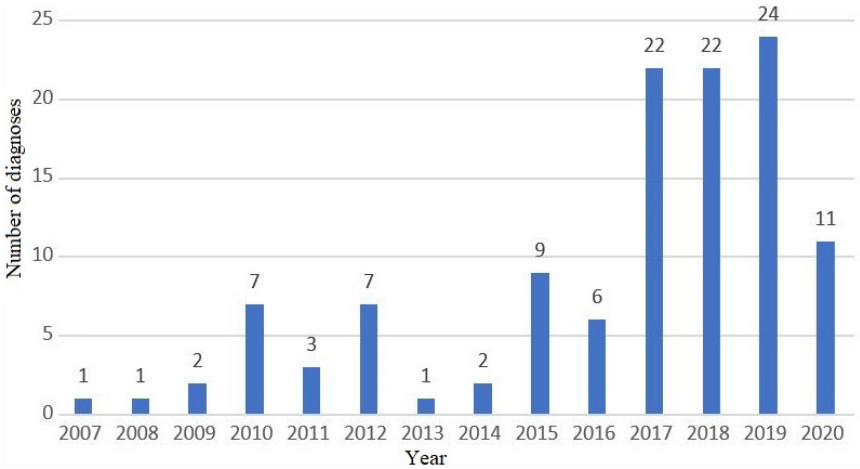

Figure 1 Annual number of rare EGFR mutations diagnosed. EGFR, epidermal growth factor receptor.

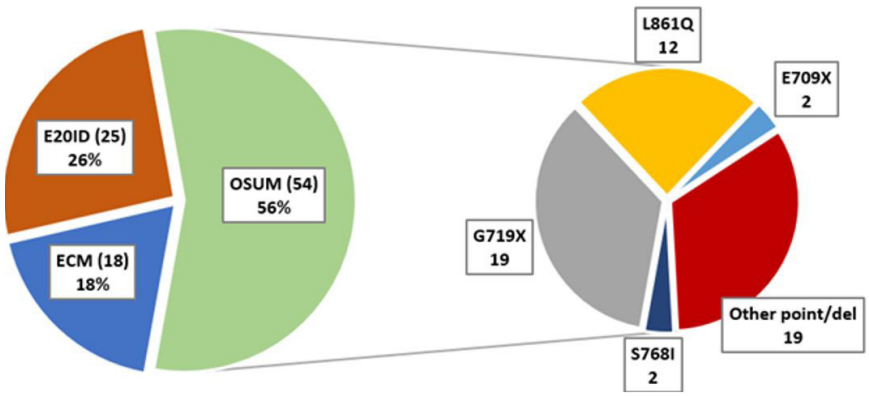

Figure S2 Distribution of rare EGFR mutations in the 97 patients stage >3b with 1st line treatment data available. E20ID, exon 20 insertion/duplication; ECM, EGFR complex mutation; OSUM, other single uncommon mutation; EGFR, epidermal growth factor receptor.

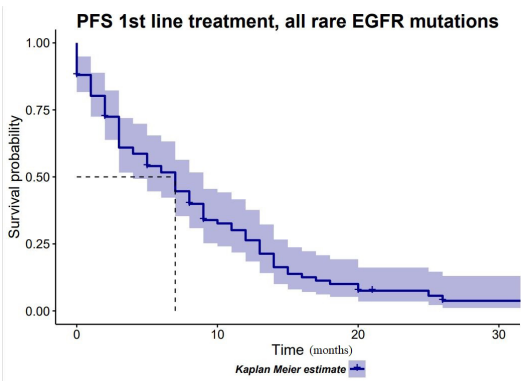

Figure S3 PFS for all uncommon EGFR mutations. PFS, progression free survival; EGFR, epidermal growth factor receptor.

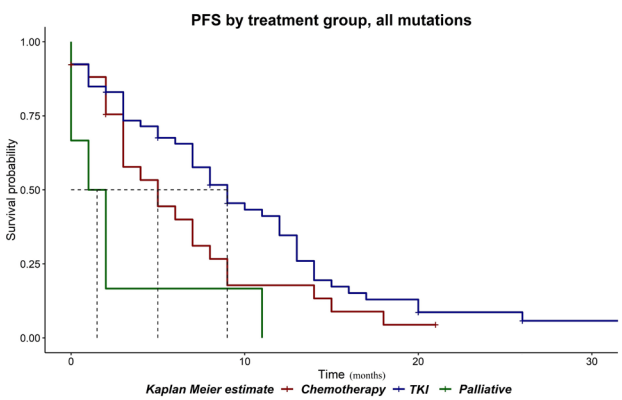

Figure S4 PFS by 1st line treatment, all mutations. PFS, progression free survival; TKI, tyrosine kinase inhibitor.

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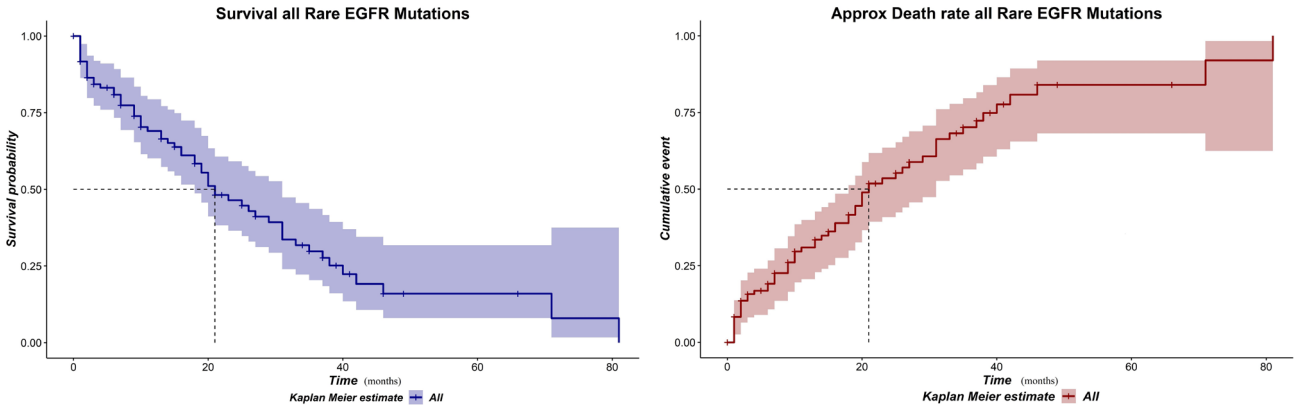

Figure S5 OS. EGFR, epidermal growth factor receptor; OS, overall survival.

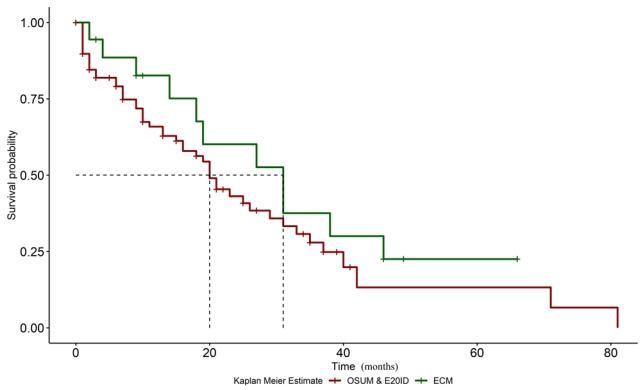

Figure S6 OS differences, complex mutations *vs.* others. OSUM, other single uncommon mutation; E20ID, exon 20 insertion/duplication; ECM, EGFR complex mutation; OS, overall survival.

Table S1 Status at end point and follow-up

	Overall	E20ID (n=34)	Other (n=85)
Status at end point (119 patients)			
Alive <6 months	37%	44%	34%
Deceased	52%	41%	56%
Lost to follow up >6 months	11%	15%	9%
Follow-up month (if >0)			
Mean	21	19	22
Median	15	15	15

E20ID, exon 20 insertion/duplication.

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Table S2 Line of treatment of >3b tumor with uncommon EGFR mutations

	Overall	E20ID	OSUM	ECM
1st line treatment	97	25	54	18
TKI among which 27 afatinib; 12 gefitinib; 8 erlotinib and 3 osimertinib; 3 others[1]	53	5	33	15
Chemotherapy (n=27) or chemo-immunotherapy (n=1) among which—13 platinum + alimta—10 platinum + taxane—1 Platinum + gemzar—1 gemzar—1 alimta—2 missing value	28	13	12	3
Palliative care	9	4	5	0
Immunotherapy (4 pembrolizumab; 1 durvalumab)	5	2	3	0
Radiotherapy (isolated cerebral metastasis)	1	1	–	–
Surgery (isolated cerebral M + ≥ post-surgery death)	1	–	1	–
2nd line treatment	50	13	32	5
TKI among which 8 TKI for TKI switch; 6 post chemotherapy; 1 post immunotherapy; 1 post radiotherapy	16	3	12	1
Chemotherapy or combo (n=2) among which 19 post TKI; 2 post chemo; 3 post immunotherapy	24	6	15	3
Palliative care (all post TKI)	3	1	2	–
Immunotherapy (6 post chemo; 1 post TKI)	7	3	3	1
Radiotherapy	0	–	–	–
3rd line treatment	27	6	12	9
TKI	4	1	1	2
Chemo or combo (only 1)	17	4	9	4
Palliative care	1		0	1
Immunotherapy	5	1	2	2
4th line treatment: 2 chemotherapy, 1 TKI, 1 palliative care				

[1], interestingly, 4 patients out of 14 checked for secondary T790M after progression under 1st or 2nd generation TKI were T790M positive; 2 of them received Osimertinib as 2nd line treatment, both of whom had rapid progression afterwards. EGFR, epidermal growth factor receptor; E20ID, exon 20 insertion/duplication; OSUM, other single uncommon mutation; ECM, EGFR complex mutation; TKI, tyrosine kinase inhibitor; TKI, tyrosine kinase inhibitor.

Table S3 ORR with 1st line treatment

	Overall	E20ID	OSUM	ECM
All 1st line treatment	45.4%	36.0%	46.3%	55.6%
TKI	56.6%	20.0%	63.6%	53.3%
Chemotherapy or combo	42.9%	53.8%	25.0%	66.7%
Palliative care	–	–	–	–
Immunotherapy	20.0%	–	33.3%	–

ORR, objective response rate; E20ID, exon 20 insertion/duplication; OSUM, other single uncommon mutation; ECM, EGFR complex mutation; TKI, tyrosine kinase inhibitor.

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Table S4 DCR with 1st line treatment

	Overall	E20ID	OSUM	ECM
All 1st line treatment	57.7%	52.0%	55.6%	72.2%
TKI	69.8%	20.0%	69.7%	73.3%
Chemotherapy or combo (n=1)	60.7%	69.2%	50.0%	66.7%
Palliative care	–	25.0%	–	–
Immunotherapy	60.0%	100.0%	33.3%	–

DCR, disease control rate. E20ID, exon 20 insertion/duplication; OSUM, other single uncommon mutation; ECM, EGFR complex mutation; TKI, tyrosine kinase inhibitor.

Appendix 1

OS by treatment in each uncommon mutation subgroup

The difference in median OS was not significant by treatment subgroup in all rare EGFR mutations. The lack of difference by treatment group remained true when analyzing subgroups which received only TKI (27 patients) vs only chemotherapy (20 patients), whatever the treatment line to avoid a hypothetical blurring effect due to the switching of treatment class (P=0.4 on log rank test) (*Figure S7*).

Among OSUM, median OS was 35 months for chemotherapy as 1st line treatment (95% CI: 9–NA); and 21 months for TKI (95% CI: 15–NA). When considering patients who received only chemotherapy or TKI, whatever the line of treatment, the median estimation for OS were respectively 35 months for chemotherapy and 33 months for TKI (*vs.* 19 months for successive chemotherapy and TKI). This difference was not significant with the log rank test (P=0.9), and survival curves show limited differences (*Figure S8*).

Among E020ID, median OS is estimated to be 21 months for chemotherapy *vs.* 20 for TKI, with non-significant differences. This was also true on analysis of chemotherapy *vs.* TKI, whatever the line of treatment (figures not shown) (*Figure S9*).

Among ECM, the very small number of patients treated with chemotherapy resulted in a non-relevant OS analysis (*Figure S10*).

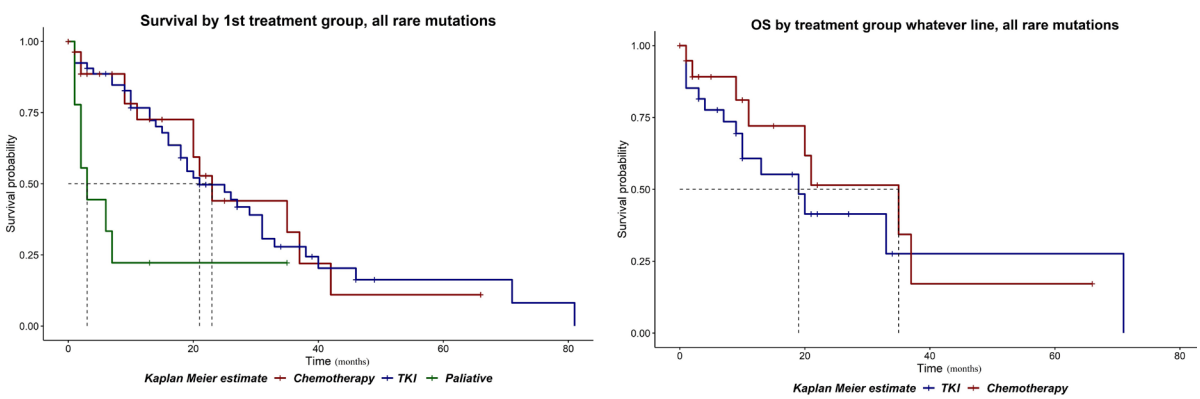

Figure S7 OS by line of treatment all rare EGFR mutations. TKI, tyrosine kinase inhibitor; OS, overall survival; EGFR, epidermal growth factor receptor.

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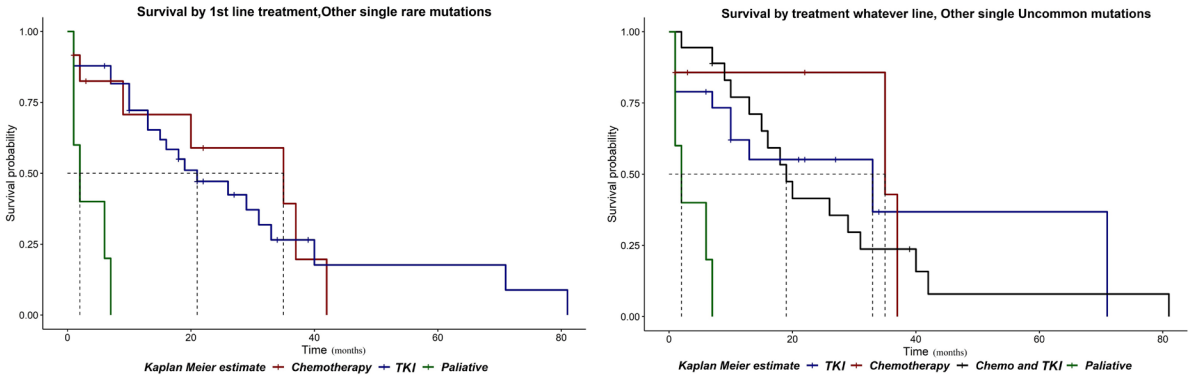

Figure S8 OS by treatment in OSUM. TKI, tyrosine kinase inhibitor; OS, overall survival; OSUM, other single uncommon mutation.

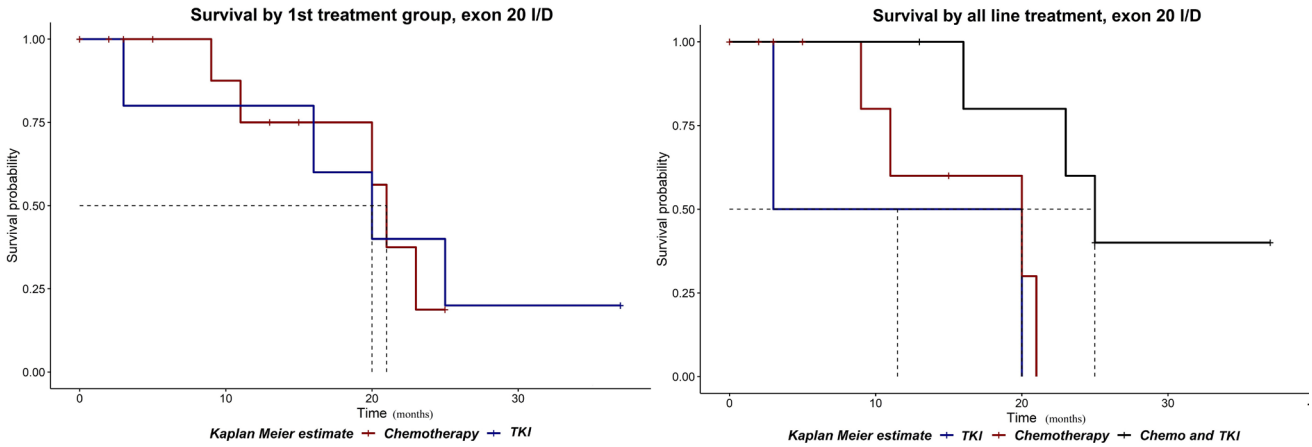

Figure S9 OS by treatment in E20ID. TKI, tyrosine kinase inhibitor; OS, overall survival; E20ID, exon 20 insertion/duplication.

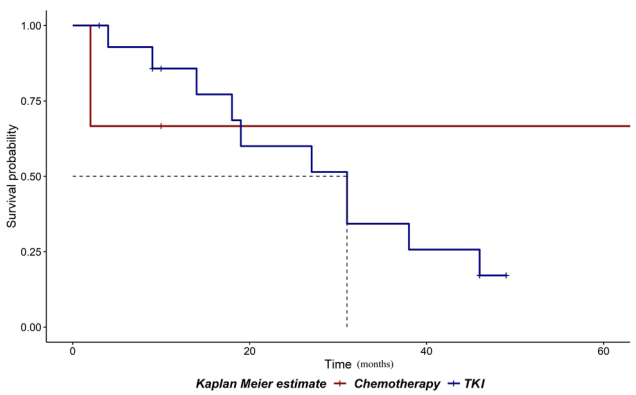

Figure S10. Survival by treatment group, ECM

Figure S10 Survival by treatment group, ECM. TKI, tyrosine kinase inhibitor; ECM, EGFR complex mutation.

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Appendix 2

Prognostic factors

Median OS in males was 19 *vs.* 23 months in females, with HR of 1.3 (95% CI: 1.1–3.4; P=0.026). Ambulatory patients at diagnosis, i.e., performance status 0, 1 or 2, were associated with better OS (*Figure S11*).

Mean OS was 31 months for performance status 0, 1 or 2 with (95% CI: 26–42) *vs.* 7 months if performance status 3 or 4 (95% CI: 2–18) with HR 3.21 (95% CI: 2.14–4.82; P<0.001) (*Figure S12*).

Interestingly, one of the last factors to be eliminated in backward stepwise selection with a P value of 0.08 was obesity (defined as BMI >30), which tended to be a non-significantly negative factor. Obese patients had a median OS of 16 (9–NA) *vs.* 21 (19–NA) months for non-obese patients. This is not the case when overweight (BMI >25) was considered. In our data, OS did not significantly differ by cerebral metastasis status (P=0.8).

Above average allelic frequency (i.e., mutational %) was not associated with better response in OS or PFS to TKI in our data. Further analysis of allelic frequency should be conducted in correlation with HES (tumor cell density). Both allelic frequency and tumor cell density were unfortunately rarely available simultaneously in our data.

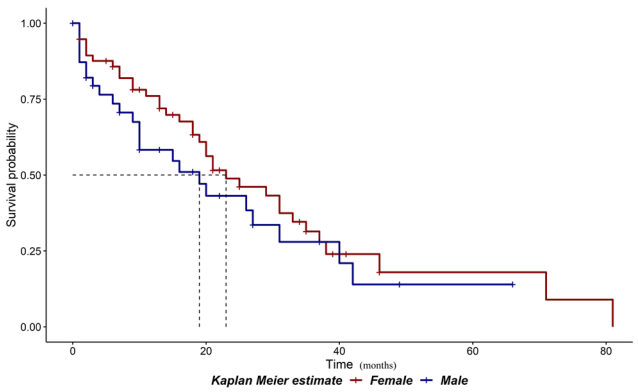

Figure S11 OS by gender. OS, overall survival.

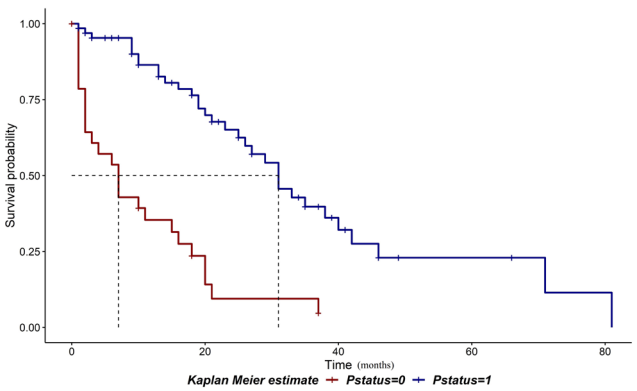

Figure S12 OS by performance status. OS, overall survival.

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Appendix 3

L861Q and G719X patients

L861Q mutant sub-cohort of 13 OSUM patients and 4 ECM with median OS of 37 months (95% CI: 10–NA) *vs.* others OSUM & ECM with 20 months (95% CI: 16–31), Log rank P=0.07; HR 0.51 with (95% CI: 0.24–1.094). Median associated PFS was 8 with (95% CI: 4–NA). ORR was 9/17 (53%) and DCR 13/17 (76%). Thus, even though it was not significant, L861Q-positive status in our cohort tended to be associated with better PFS and OS than other uncommon EGFR mutations (*Figure S13*).

The G719X mutant sub-cohort of 18 OSUM and 6 ECM had median OS of 19 months (95% CI: 7–42) *vs.* 21 months in other OSUM and ECM (95% CI: 7–42; Log rank P=0.2; HR 1.42 with 95% CI: 0.8–2.5). Median associated PFS was 7 (95% CI: 4–16). ORR was 14/24 (58%), and DCR 16/24 (67%). Thus, even though it was not significant, G719X-positive status tended to be associated with lower PFS and OS than other uncommon EGFR mutations (*Figure S14*).

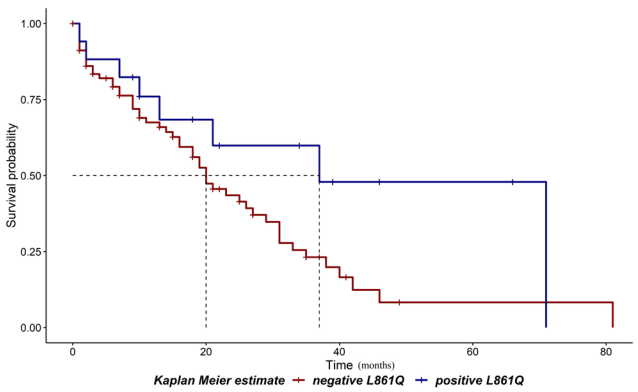

Figure S13 OS by L861Q status. OS, overall survival.

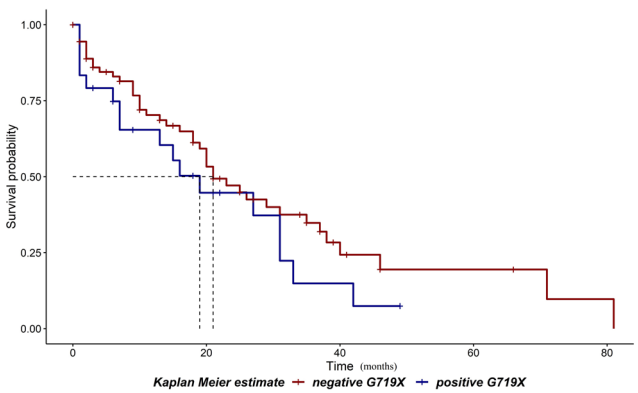

Figure S14 OS by G719X status. OS, overall survival.

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Appendix 4

Immunotherapy as 1st line treatment

In our data, there were 5 uncommon EGFR mutant stage IV tumors (3 OSUM and 2 E20ID) treated with immmunotherapy (4 with pembrolizumalb and 1 with durvalumab). All were PDL1 positive, and 80% were PDL1 >50%. In the 2 cases with compassionate use, death occurred after 1 and 5 months. There were 0% DRR and 40% DCR with 1 hyperprogression and 2 PFS of 23 and 26 months in 2 cases of association with radiotherapy in a cerebral oligo-metastatic location. The non-compationate use patients were still alive after 18, 20 and 36 months, and underwent a 2nd line treatment with either chemotherapy (n=2) or TKI (n=1).

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