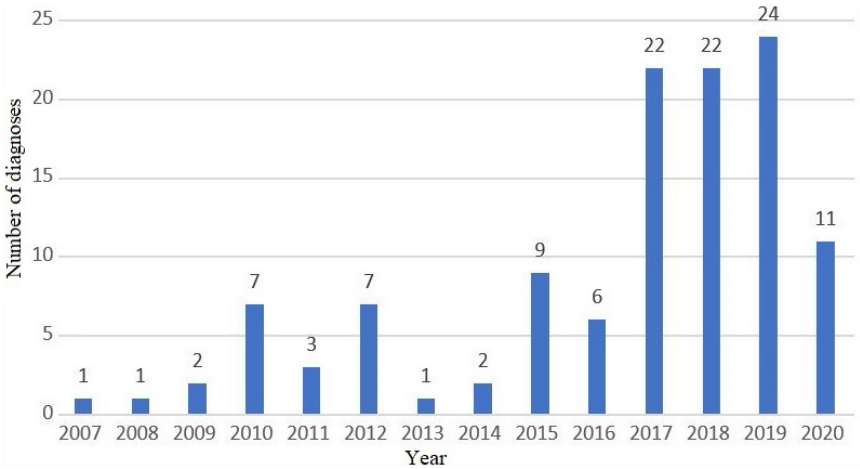

Figure 1 Annual number of rare EGFR mutations diagnosed. EGFR, epidermal growth factor receptor.

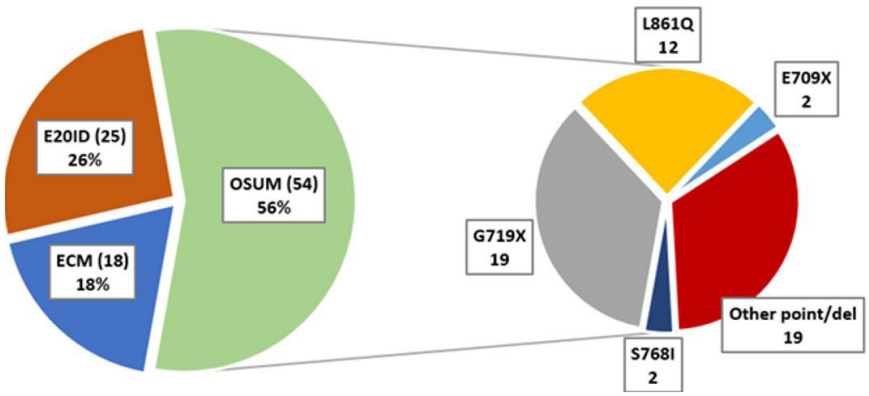

Figure S2 Distribution of rare EGFR mutations in the 97 patients stage >3b with 1st line treatment data available. E20ID, exon 20 insertion/duplication; ECM, EGFR complex mutation; OSUM, other single uncommon mutation; EGFR, epidermal growth factor receptor.

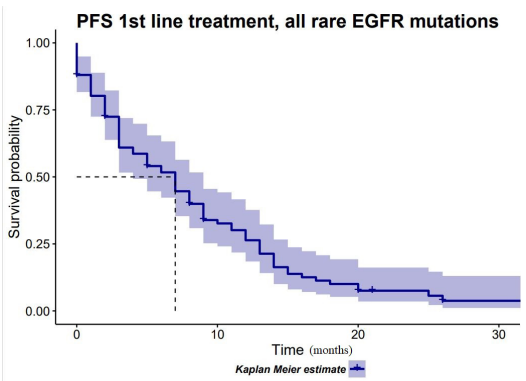

Figure S3 PFS for all uncommon EGFR mutations. PFS, progression free survival; EGFR, epidermal growth factor receptor.

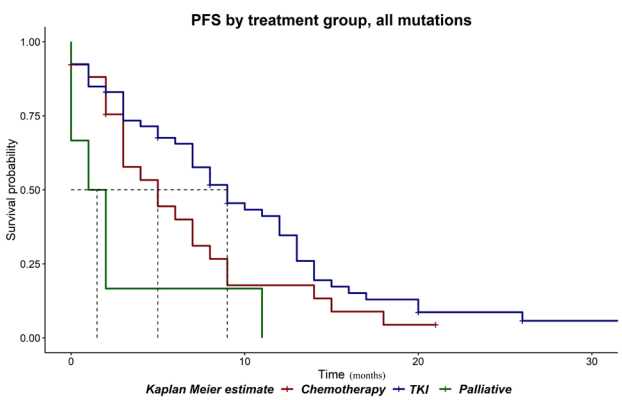

Figure S4 PFS by 1st line treatment, all mutations. PFS, progression free survival; TKI, tyrosine kinase inhibitor.

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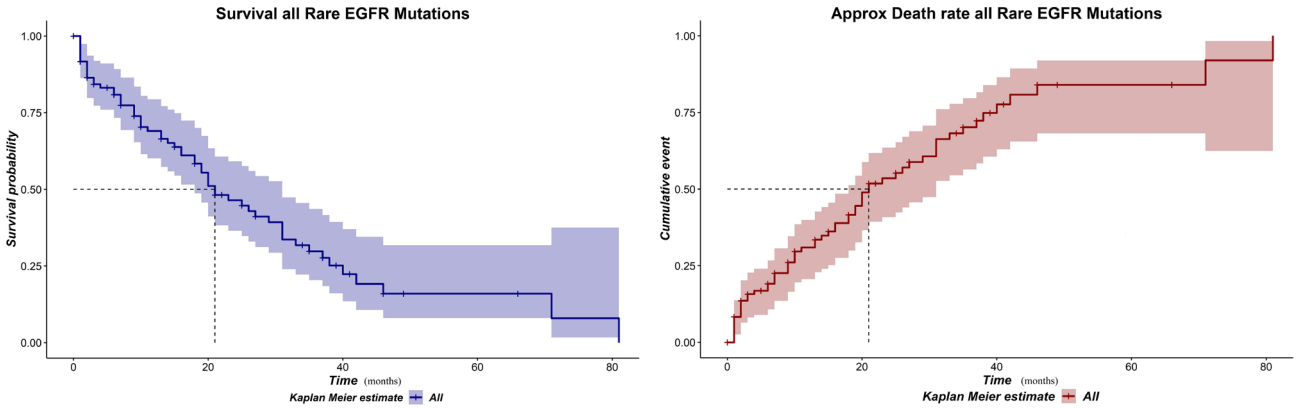

Figure S5 OS. EGFR, epidermal growth factor receptor; OS, overall survival.

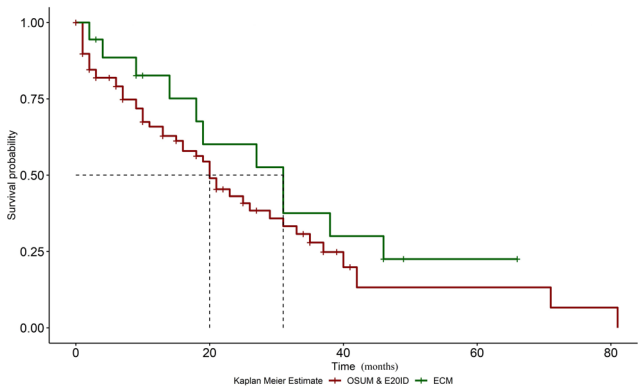

Figure S6 OS differences, complex mutations *vs.* others. OSUM, other single uncommon mutation; E20ID, exon 20 insertion/duplication; ECM, EGFR complex mutation; OS, overall survival.

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*).

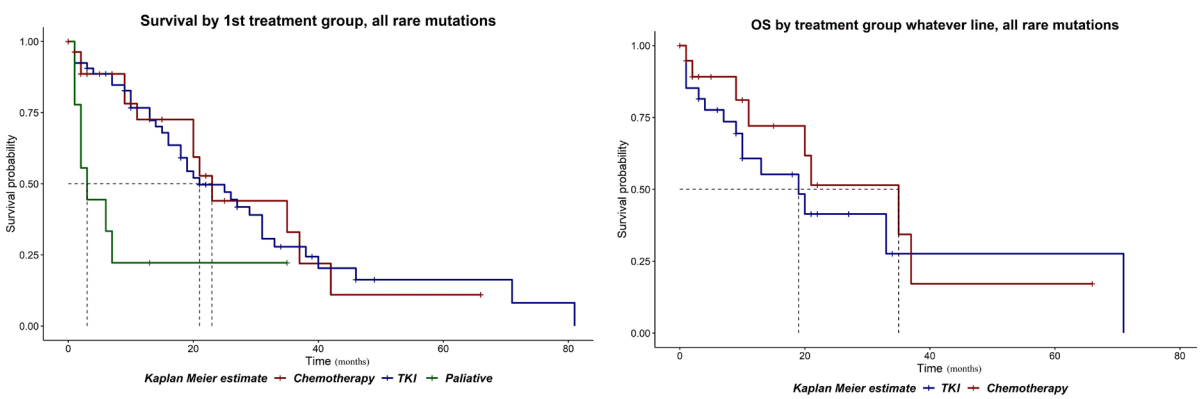

Figure S7 OS by line of treatment all rare EGFR mutations. TKI, tyrosine kinase inhibitor; OS, overall survival; EGFR, epidermal growth factor receptor.

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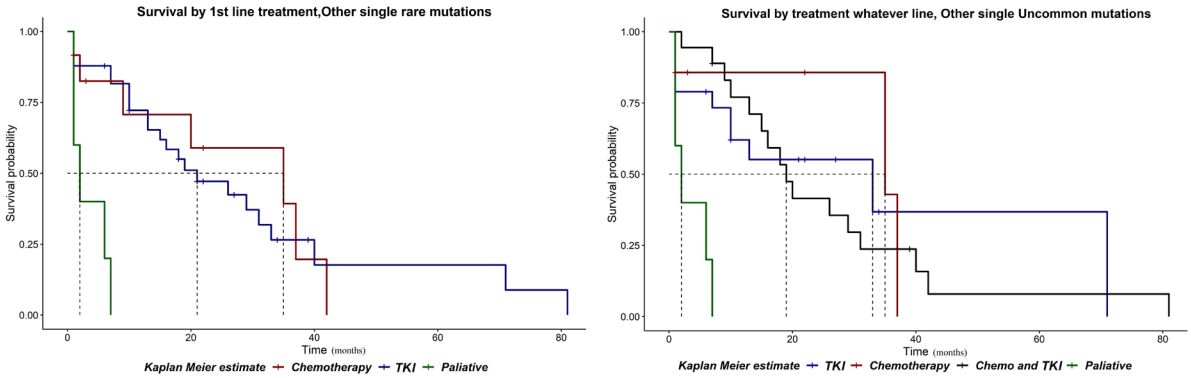

Figure S8 OS by treatment in OSUM. TKI, tyrosine kinase inhibitor; OS, overall survival; OSUM, other single uncommon mutation.

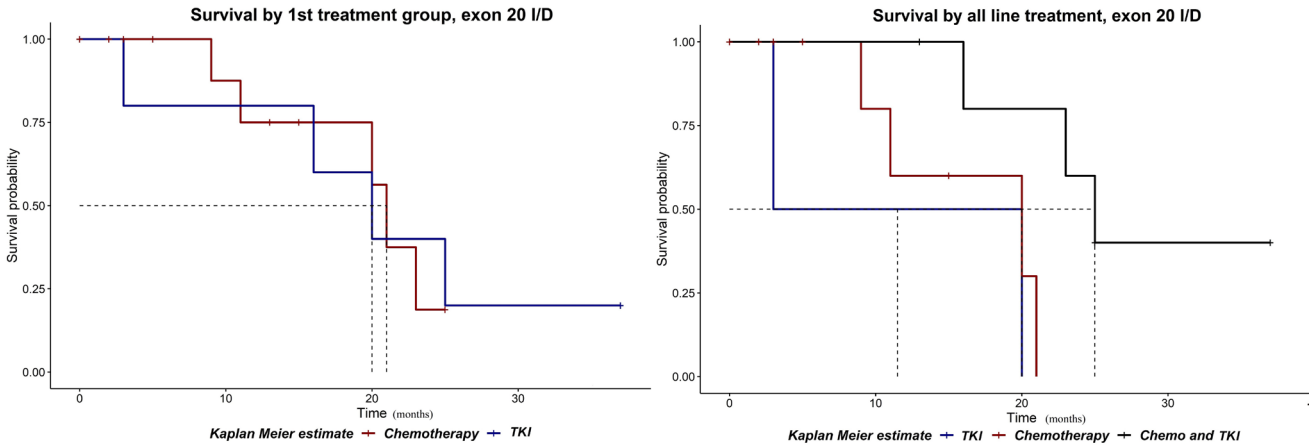

Figure S9 OS by treatment in E20ID. TKI, tyrosine kinase inhibitor; OS, overall survival; E20ID, exon 20 insertion/duplication.

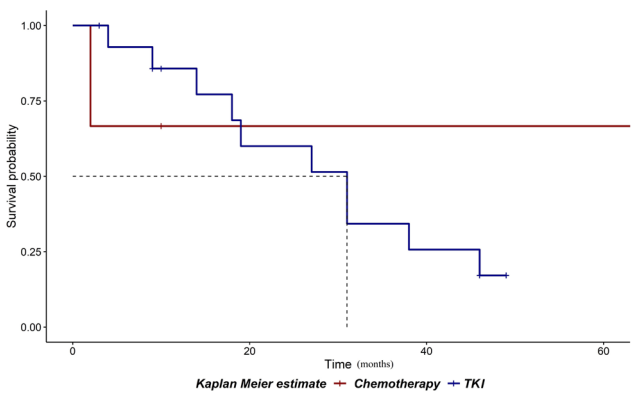

Figure S10. Survival by treatment group, ECM

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

https://dx.doi.org/10.21037/jtd-21-1924

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.

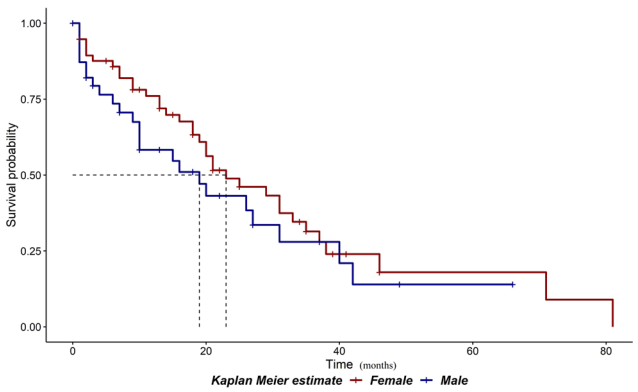

Figure S11 OS by gender. OS, overall survival.

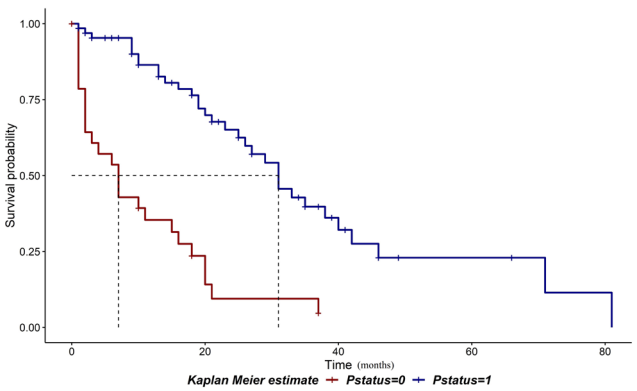

Figure S12 OS by performance status. OS, overall survival.

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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*).

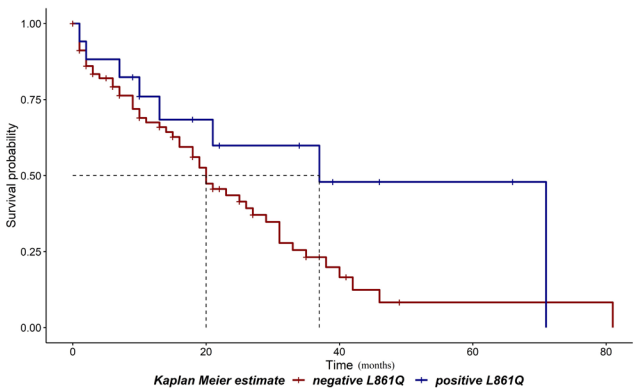

Figure S13 OS by L861Q status. OS, overall survival.

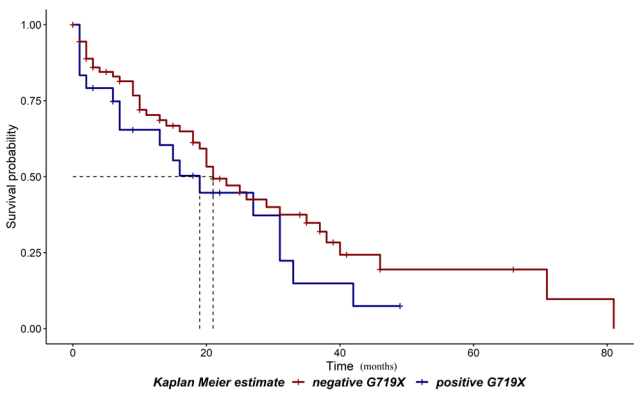

Figure S14 OS by G719X status. OS, overall survival.

https://dx.doi.org/10.21037/jtd-21-1924

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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