Abstract # 1585

Genomic and immune characteristics of EGFR subtypes in non-small cell lung cancer (NSCLC)

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BACKGROUND

- While EGFR-mutant NSCLC tumors generally are resistant to PD-1/PD-L1 inhibitors, a small subset of patients can have durable responses.[1,2]
- EGFR tumors demonstrate significant molecular heterogeneity, especially with respect to mutation subtypes.
- A small number of studies suggest better outcomes with checkpoint inhibitors in patients with tumors possessing uncommon EGFR mutations[3] or L858R mutations,[1] however data on this are still limited.
- There is a lack of clarity on the genomic and immune profiles of EGFR mutation subtypes, and further elucidation of this may help optimally identifying patients likely to respond to immune-based therapies.

METHODOLOGY

- Molecular profiles of 5,510 lung adenocarcinoma specimens were obtained using next-generation sequencing at Caris Life Sciences on DNA (592 genes or WES) and RNA (WTS).
- PD-L1 IHC testing was performed using the 22c3 Ab clone (Dako). Tumors were classified by PD-L1 positivity (≥ 1%) and by PD-L1 high (≥ 50%).
- Tumor mutational burden (TMB) was determined by counting nonsynonymous missense, nonsense, in-frame insertion/deletion and frameshift mutations found per tumor. TMB high was defined as ≥ 10 mutations/Mb.
- QuantiSeq was used to calculate immune cell fractions in the tumor microenvironment using transcriptome data.[4]
- PD-L1 expression, TMB, TP53 co-mutations, and immune cell fractions were analyzed by EGFR subtype and compared to wild-type (WT) tumors. Chi-square or Fisher's exact tests were used with correction for multiple comparisons.

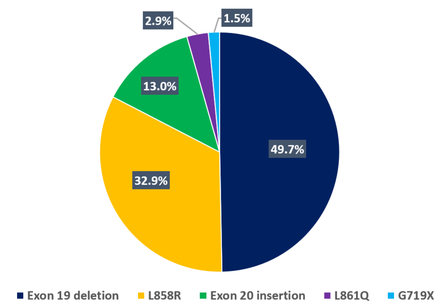
RESULTS

Table 1. Description of study cohort (N = 5510)

	Total N	Median Age (min, max)	Female n (%)	Male n (%)
EGFR WT	4719	69 (24, 97)	2519 (53.4%)	2200 (46.6%)
EGFR Subtype				
Exon 19 deletion	393	66 (29, 95)	283 (72.0%)	110 (28.0%)
L858R	260	72 (42, 93)	183 (70.4%)	77 (29.6%)
Exon 20 insertion	103	64 (29, 90)	69 (67.0%)	34 (33.0%)
L861Q	23	73 (55, 85)	20 (87.0%)	3 (13.0%)
G719X	12	67 (45, 79)	8(66.7%)	4 (33.3%)

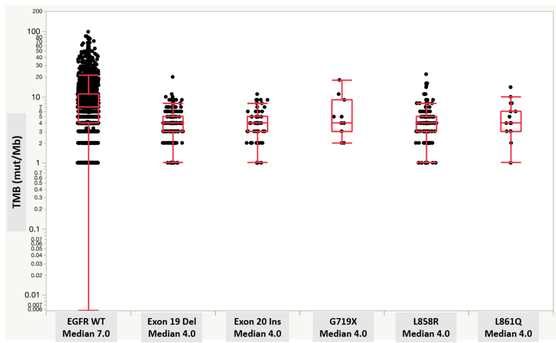
- Of the total cohort of 5,510 patients with lung adenocarcinomas, 791 (14.4%) were EGFR-mutated. Women were greater represented in the overall cohort, and especially among patients with EGFR-mutated disease.

Figure 1. Distribution of EGFR subtypes



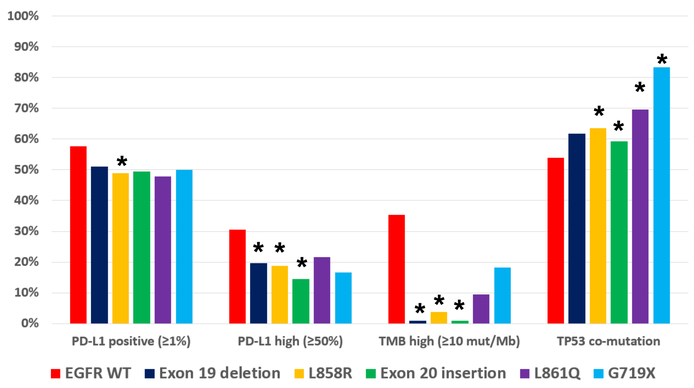
- Among EGFR tumors, Exon 19 deletions were most common (49.7%), followed by L858R, (32.9%), exon 20 insertions (13.0%), L861Q (2.9%), and G719X (1.5%).

Figure 2. TMB distribution among EGFR subtypes as compared to WT



- Median TMB was lower in all EGFR mutation subtypes as compared to WT.

Figure 3. Immunotherapy associated biomarkers among EGFR subtypes as compared to WT



* *q-value < 0.05 when compared to EGFR WT (corrected for multiple comparisons)*

- EGFR subtypes with PD-L1 positivity (≥1%) did not differ versus WT, except for L858R which had a significantly lower percentage PD-L1 positive.
- Exon 19 deletion, L858R, and exon 20 insertion tumors were significantly less likely to be PD-L1 high (≥50%) or have high TMB (≥10 mut/Mb) versus WT. Among EGFR subtypes, L861Q (9.5%) and G719X (18.2%) had the greatest percentage with high TMB.
- TP53 co-mutations occurred frequently in EGFR cases, especially among L861Q (69.6%) and G719X (83.3%) tumors.

Table 2. Tumor immune cell type fractions among EGFR subtypes as compared to WT

	CD8+ T cells	CD4+ T cells	Neutrophils	Macrophages M2
	Median % immune cell fraction			
EGFR WT	0.7	0.0	5.5	5.5
EGFR Subtype				
Exon 19 deletion	**0.3***	**0.6***	**8.0***	**6.4***
L858R	**0.4***	**0.8***	**7.3***	**6.9***
Exon 20 insertion	0.3	**1.3***	**7.8***	**6.7***
L861Q	0.6	1.7	7.4	5.8
G719X	0.2	1.1	6.4	4.3

* *q-value < 0.05 when compared to EGFR WT (corrected for multiple comparisons)*

- Exon 19 deletion and L858R tumors had significantly less CD8+ and greater CD4+ T cell fractions as compared to WT.
- Neutrophils and M2 macrophages cell fractions were significantly greater in exon 19 deletion, L858R, and exon 20 insertion tumors as compared to WT.

References

1. Hastings et al., Ann Oncol 2019;30:1311-20.
2. Mazieres et al., Ann Oncol 2019; 30:1321-8.
3. Yamada et al., Cancer Med 2019; 1521-9.
4. Finotello et al., Genome Med 2019; 11:34

CONCLUSIONS

- Most subtypes of EGFR have profiles consistent with decreased immunogenicity.
- In particular, exon 19 deletion, L858R, and exon 20 insertion tumors are less likely to be PD-L1 high or TMB high as compared to WT. In addition, exon 19 deletion and L858R tumors have lower CD8+ T cell fractions as compared to WT.
- However, L861Q and C719X tumors have a greater percentage with high TMB or TP53 co-mutations. Such characteristics in these uncommon EGFR subtypes may correlate with responsiveness to immune-based therapies and warrants further investigation.