Acquired EGFR resistant mutations in Non-Small Cell Lung Cancer (NSCLC).

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Background:

EGFR mutations are present in more than 10% of patients (pts) with NSCLC in the US. While EGFR with tyrosine kinase inhibitors (TKIs) are effective, acquired resistance is expected. Known mechanisms include acquired EGFR mutations (e.g. 718V, c797x, 724s, 721s or T790M); copy number amplifications in MET, ERBB2, and PIK3CA; gene fusion events; and histological transformation. We herein present the prevalence of resistance mutations in the largest reported cohort of EGFR mutant NSCLC.

Methods:

Non-small cell lung cancer (NSCLC) tumor samples were submitted to Caris Life Sciences (Phoenix, AZ) for NextGen Sequencing (NextSeq, 592 Genes) and whole exome sequencing (NovaSeq, WES). PD-L1 expression was tested by IHC using 22c3 (Dako) and TPS scores were reported (cutoff ≥1). TMB was measured by totaling somatic mutations (TMB-high cut-off ≥ 10 mutations per MB), genomic loss of heterozygosity (gLOH) was determined by WES.

Figure 1: Total cohort of NSCLC tumors and EGFR mutation distribution.

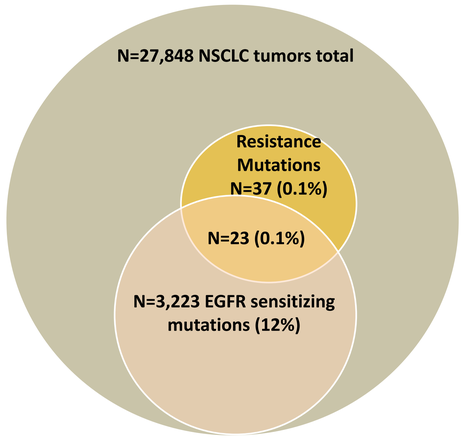

Table 1: Patient demographics

EGFR mutation	Co-occurring T790M	Male	Female	Total	Median age
C797	26	16	22	38	63.5
L718	3	5	6	11	72
G724	1	2	5	7	73
G721	0	2	2	4	61.5
Total	**30**	**25**	**35**	**60**	**65**

Results

Figure 2A: Oncoprint for EGFR L718 mutated tumors (N=11)

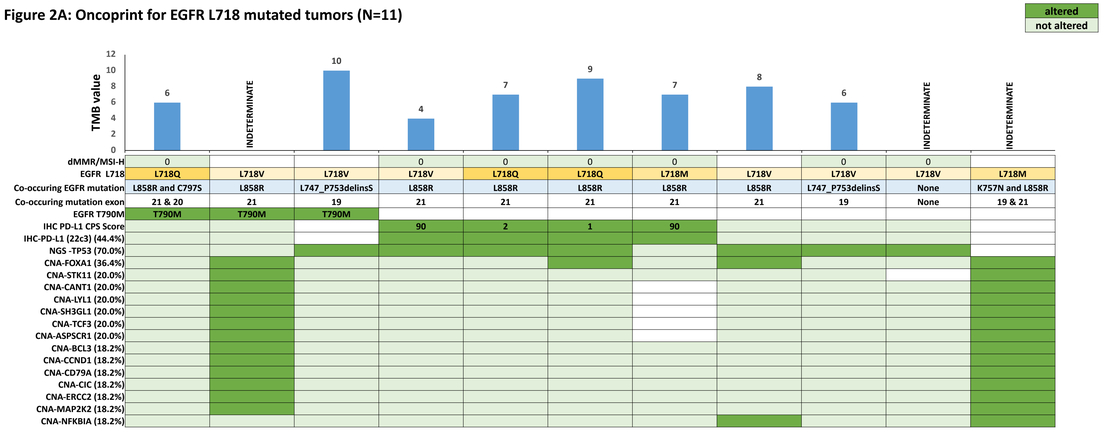

Figure 2B: Oncoprint for C797, G724 and G721 mutated tumors (N=49)

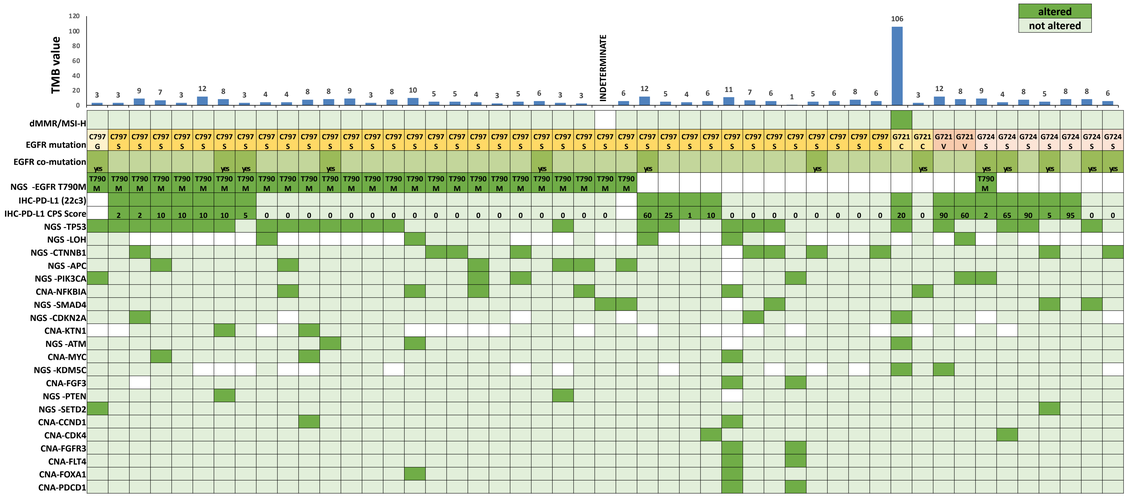

Figure 3: IO marker prevalence and other co- alterations in EGFR resistance mutants.

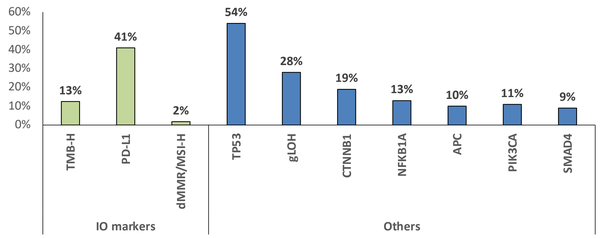

Table 2: Summary table of top alterations in acquired EGFR mutated cohort.

EGFR MT	N	%	T790M co-mt	PD-L1	TP53	LOH
C797	38	1.2	26/38 (68%)	11/36 (30%)	20/38 (53%)	4/14 (28%)
L718	11	0.3	3/11 (27%)	4/9 (44%)	7/10 (70%)	0/1 (0%)
G724	7	0.2	1/7 (14%)	5/7 (71%)	3/7 (43%)	0/1 (0%)
G721	4	0.1	0/4 (0%)	3/4 (75%)	2/4 (50%)	1/2 (50%)
Total	**60**			**23/56 (41%)**	**32/59 (54%)**	**5/18 (28%)**

Conclusions

- Of 27,848 NSCLC tumors, 3,223 (12%) had an EGFR sensitizing mutation, 60 (0.2%) had common missense resistance mutations (C797, L718, G724 and G721).
- L718 mutations co-occurred with either L858R (8/11) or exon 19 (3/11). Additionally, 3/11 co-occured with T790M mutations.
- In the resistance mutant cohort, 13% were TMB-H (≥10 Mt/Mb), 41% were PDL1-H and 2% were dMMR/MSI-H.
- Other co-alterations include TP53 (53%), gLOH by WES (28%), CTNNB1 (19%), NFKB1A (13%), APC (10%), PIK3CA (11%) and SMAD4 (9%).
- Acquired resistance in EGFR mutant NSCLC is very heterogeneous and their frequency is still low most likely due to lack of enough sequencing of EGFR resistant tumors . These data support the NGS evaluation of patients with resistant EGFR mutant lung cancers.