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GEORGETOWN UNIVERSITY

Updated Molecular Analysis of *MET* Exon 14 Skipping Mutations (METex14) in Non-Small Cell Lung Cancer (NSCLC)

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Background

- *MET* is a proto-oncogene that plays a central role in cell proliferation and survival
- Somatic mutations impacting exon 14 alternative splicing can lead to skipping the transcription of the Y1003 loci which is critical for the regulation of MET activation
- *MET* exon 14 skipping mutations (*MET*ex14) are now established therapeutic targets in non-small cell lung cancer (NSCLC)
- There is notable heterogeneity in *MET*ex14, which occurs in smokers and non-smokers and both squamous (Sq) and non-squamous (nSq) histology
- We aimed to explore the heterogeneous mutational landscape within *MET*ex14 NSCLC by specific mutation, histology, and smoking status

Objectives and Methods

- NSCLC samples were analyzed at Caris Life Sciences (Phoenix, AZ) with DNA-based next-generation sequencing (NGS; 592 genes, NextSeq) or whole-exome sequencing (NovaSeq) and with RNA-based whole-transcriptome sequencing (WTS, NovaSeq)
- *MET*ex14 events were detected by WTS, and biomarkers with counts ≥ 5 and co-mutations ≥ 2% are displayed
- For all *MET*ex14 events, protein change information was gathered using WES platform; protein change groups with sample size ≥ 5 are displayed
- PD-L1 expression was determined by immunohistochemistry (IHC) with the Dako 22C3 clone
- High tumor mutational burden (TMB) was defined as ≥ 10 mutations/Mb
- Wilcoxon or Fisher's exact were used to determine statistical significance (p without and q with multi-comparison correction)
- Immune cell fraction (quanTIseq) and pathway analysis (ssGSEA) were informed by WTS analysis

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Results

*MET*ex14 Events by WTS and WES

Features/ Cohort	METex14skip+ (n=711)	METex14skip- (n=28060)
Fusion Variant-MET	100.00	0.00
NGS-MET	90.13	0.16
IHC-PD-L1 (22c3)	80.76	56.17
NGS-TP53	43.41	67.65
CNA-MDM2	18.81	1.89
CNA-HMGA2	13.45	1.01
CNA-CDK4	9.33	1.52
TMB High	9.03	37.48
CNA-WIF1	7.06	0.64
CNA-LGR5	6.36	0.56
NGS-POT1	5.00	1.46
NGS-NF1	4.90	8.93
NGS-BRCA2	4.01	1.75
CNA-LRIG3	3.45	0.51
CNA-MET	2.87	0.93
NGS-KRAS	2.54	27.94
NGS-CDKN2A	2.13	10.86

Table 1. *MET*ex14 Events by WTS
(Biomarkers with counts ≥ 5 and co-mutations ≥ 2% displayed)

Features	D1028H	D1028N	c.3082+2T>C	D1028Y	c.3082+1G>T	c.3082+1G>A	c.3082+3A>T	c.3082+3A>G	c.3082+2T>A	c.3082+1delG	c.3082+1G>C	c.2942-1G>A	G344R	c.3082+2T>G
Fusion Variant-MET	100.00	100.00	100.00	100.00	100.00	100.00	100.00	100.00	100.00	100.00	100.00	100.00	100.00	100.00
NGS-MET	100.00	100.00	100.00	100.00	100.00	100.00	100.00	100.00	100.00	100.00	100.00	100.00	100.00	100.00
IHC-PD-L1 (22c3)	90.20	81.13	72.73	86.21	83.33	85.19	68.18	70.00	100.00	90.91	91.67	83.33	33.33	100.00
NGS-TP53	43.40	45.10	29.41	46.67	34.48	48.15	39.13	60.00	33.33	41.67	27.27	0.00	16.67	33.33
CNA-MDM2	20.75	11.32	36.36	13.33	20.69	17.24	8.70	10.53	0.00	8.33	33.33	28.57	33.33	33.33
CNA-HMGA2	20.45	12.20	24.00	24.00	15.38	12.00	11.11	7.69	0.00	0.00	27.27	33.33	40.00	25.00
CNA-CDK4	9.43	7.55	11.76	10.00	6.67	10.34	8.70	5.26	0.00	8.33	16.67	42.86	0.00	0.00
TMB High	9.09	7.55	8.82	9.68	10.34	3.70	4.35	15.00	0.00	9.09	16.67	14.29	0.00	16.67
CNA-WIF1	5.56	0.00	0.00	20.00	0.00	0.00	33.33		0.00	0.00	33.33	0.00	0.00	0.00
CNA-LGR5	0.00	0.00	0.00	0.00	16.67	0.00	0.00		0.00	0.00	33.33	50.00	0.00	0.00
NGS-POT1	5.56	3.92	5.88	3.33	6.67	3.45	13.04	5.00	0.00	0.00	16.67	14.29	0.00	0.00
NGS-NF1	9.76	2.50	7.69	5.00	13.64	0.00	5.00	5.00	12.50	10.00	0.00	0.00	33.33	0.00
NGS-BRCA2	3.77	1.89	2.94	6.45	3.33	3.57	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
CNA-LRIG3	0.00	0.00	0.00	8.33	0.00	0.00	0.00		0.00	0.00	33.33	0.00	0.00	0.00
CNA-MET	1.89	3.77	2.94	0.00	3.33	3.45	0.00	5.26	10.00	8.33	0.00	0.00	0.00	0.00
NGS-KRAS	3.64	0.00	0.00	3.23	3.33	0.00	8.70	5.00	0.00	0.00	0.00	14.29	0.00	0.00
NGS-CDKN2A	1.85	1.89	0.00	0.00	3.45	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
Number of Specimens	55	53	34	31	30	29	23	20	12	12	12	7	6	6

Table 2. Protein Change by WES
Protein change groups with sample size ≥ 5 are displayed)

Out of 28,711 NSCLC samples tested, there were 711 unique *MET*ex14 samples identified with notable heterogeneity by mutation type, co-alteration, and histology.

Of those 581 *MET*ex14 samples with reported histology:

- 79 (11.1%) were squamous
- 478 (67.2%) were non-squamous
- 24 (3.2%) were adenosquamous

288 distinct *MET*ex14 mutations were identified; common mutations were D1028H (8.1%), D1028N (7.8%), c.3082+2T>C (5.0%), D1028Y (4.6%), and c.3082+1G>T (4.4%).

Co-mutated *TP53* was common (43.4%): 60.0% of *MET* c.3082+3A>G vs 16.7% of *MET* G344R.

Co-amplified CDK4 was found in 9.3%, with 42.9% in *MET* c.2924-1G>A vs 6.7% in *MET* c.3802+1G>T (p<0.05).

High TMB was seen in 9%; median TMB ranged from 2 mt/Mb in *MET* c.3082+2T>A to 6.5 mt/Mb in *MET* c.3082+2T>G (p<0.05).

PD-L1 ≥ 1% was seen in 80.8% compared to 56.2% in *MET*ex14-WT(p<0.05), and median PD-L1 tumor proportion score (TPS) 0% in *MET* G344R to 75% in *MET* c.3082+2T>A (p<0.05).

Smoking Status

Smoking status was available for 120 cases: 88% were smokers and 12% were nonsmokers.

Wnt, Hedgehog, and Notch signaling were enriched in nSq (q<0.05) while upregulation of KRAS signaling, Epithelial-Mesenchymal Transition, and angiogenesis pathways were enriched in smokers with *MET*ext14 NSCLC (q<0.2).

Higher estimates of neutrophils and lower estimates of M2 macrophages, NK cells, and CD8+ T-cells were observed in Sq-NSCLC. PD-L1, PD-1, HAVCR2, IDO-1 and IFN-γ expression were higher in nSq than Sq-NSCLC (q<0.05).

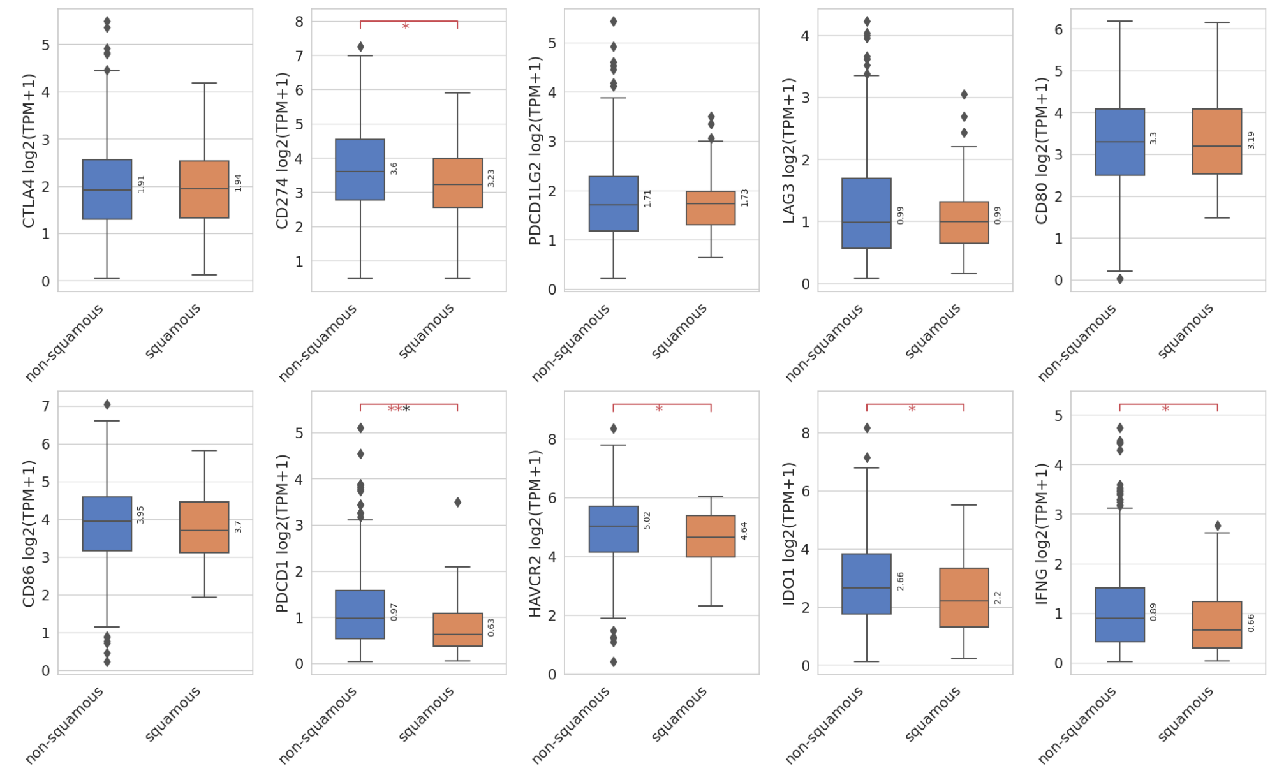

Figure 1: Immune Checkpoint Expression: Non-squamous vs Squamous NSCLC

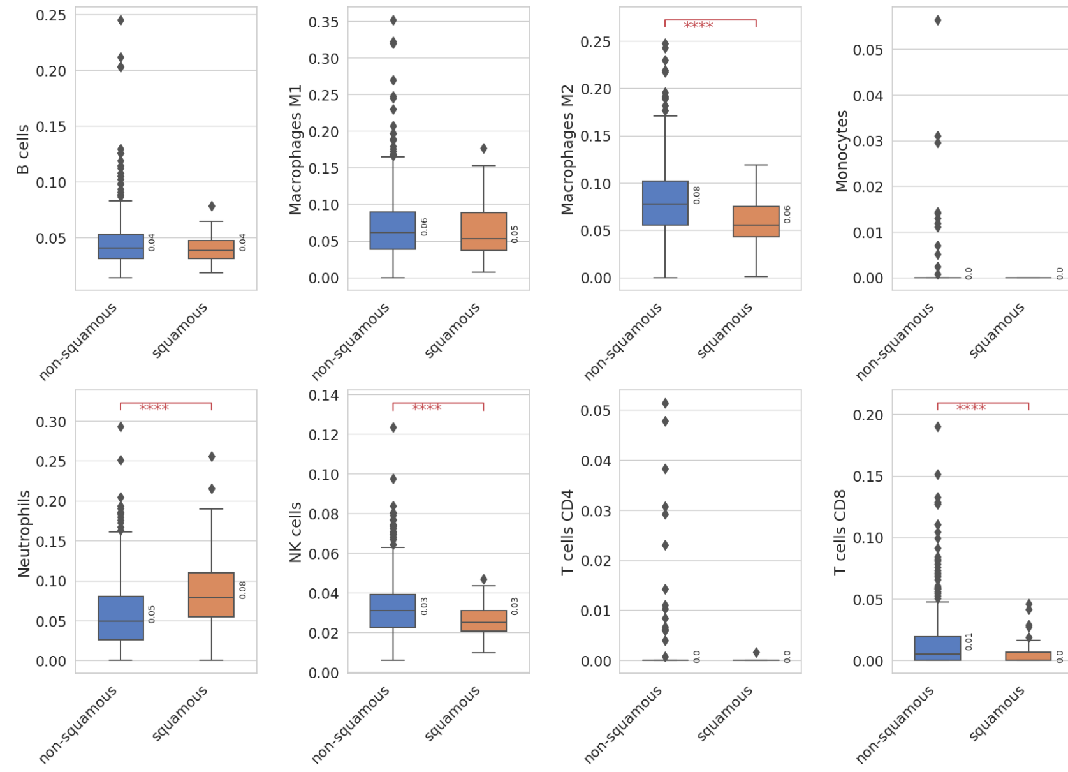

Figure 2: Immune Cell Infiltration: Non-squamous vs Squamous

Co-Mutation by Histology

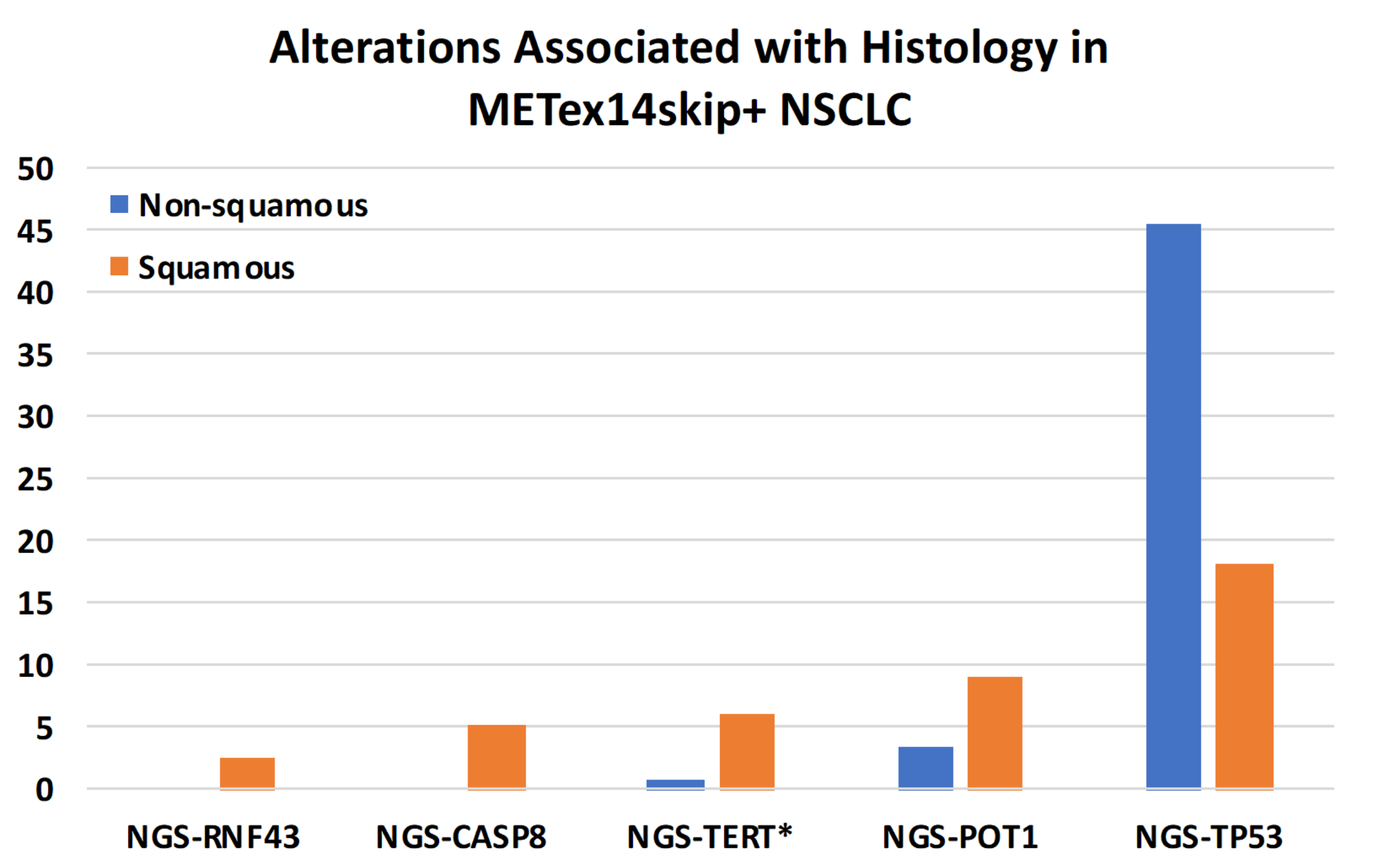

Figure 3. Genomic Alterations of Mutated *MET*ex14 by Histology

Co-mutations varied by histology: in Sq-NSCLC, 18.18% had *TP53* mt (q<0.05), 8.97% had *POT1* mt (p<0.05), 6.06% had *TERT* mt (p<0.05), 5.13% *CASP8* mt (q<0.05), and 2.53% *RNF43* mt (p<0.05), while in nSq-NSCLC, 45.51% had *TP53* mt, 3.38% had *POT1* mt, 0.87% had *TERT* mt, and 0% in *CASP8* and *RNF43* mt.

Conclusions

There is significant heterogeneity within *MET*ex14 NSCLC, with differences in co-mutations, TMB, and PD-L1 expression noted among different *MET*ex14 mutations. While *MET*ex14 is detected in both squamous and non-squamous NSCLC, there are differences in the enrichment of oncogenic pathways, which may explain the heterogeneity in response to various treatments. Future studies investigating specific *MET*ex14 alterations may allow more granular personalization of treatment for patients with *MET*ex14 NSCLC.

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