Analysis of *MET* Exon 14 Skipping Mutations in Non-Small Cell Lung Cancer (NSCLC) by Histology and Specific Mutation

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Background

MET exon 14 skipping mutations (METex14) join a growing list of viable therapeutic targets in advanced NSCLC. Several unique features distinguish METex14 from other established targets. METex14 has been characterized as a tumor-agnostic genomic alteration, though most frequently reported in lung adenocarcinoma. However, METex14 represents a family of mutations (mt), not a single alteration, and there is notable heterogeneity in histology. The degree and significance of heterogeneity within METex14 have not been well characterized.

Objectives and Methods

NSCLC tissue samples were analyzed with DNA-based next-generation sequencing (NGS; 592 genes, NextSeq) or whole-exome sequencing (NovaSeq), RNA-based whole transcriptome sequencing (WTS, NovaSeq), and immunohistochemistry (IHC) at Caris Life Sciences (Phoenix, AZ). PD-L1 expression utilized the 22C3 clone (Dako); TMB-high was defined as ≥ 10 mt/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. Overall survival was calculated from date of tissue collection to last contact from insurance claims data and compared using Kaplan-Meier method.

Results

A total of 440 METex14 cases were identified: 49 (11.1%) with squamous histology, 381 (86.6%) with non-squamous histology, and 10 (0.2%) with adenosquamous histology. A total of 147 distinct METex14 mutations were detected.

The most common METex14 mutations were D1028H (8.4%), D1028N (7.0%), c.3082+2T>C (5.7%), D1028Y (5.2%), and c.3082+1G>A (4.5%).

Co-mutations in TP53 were common (43.9%) but varied by specific METex14 mutation; TP53 co-mutations were observed in 53.9% of c.3082+3A>T but only 21.1% of c.3082+1G>T.

Biomarker	N of co-altered biomarker	co-alteration percentage [100%]
NGS-MET	380	88.37
IHC-PD-L1 (22c3)	351	82.20
NGS-TP53	183	43.88
CNA-MDM2	77	18.51
CNA-HMGA2	48	13.68
CNA-CDK4	44	10.43
TMB High	36	8.61
NGS-RB1	22	8.21
CNA-WIF1	12	7.02
NGS-HRR	15	6.58
CNA-LGR5	11	6.32
NGS-NF1	18	6.19
NGS-POT1	22	5.25
NGS-PIK3CA	20	4.68
NGS-BRCA2	15	3.59
NGS-SMAD4	15	3.52
CNA-LRIG3	6	3.43
NGS-ARID1A	8	3.29
CNA-FGF3	12	3.02
CNA-FGF4	12	2.91
NGS-ARID2	12	2.88
CNA-FGF19	11	2.66
CNA-MET	11	2.61
NGS-CDKN2A	11	2.59
NGS-CHEK2	10	2.48
CNA-CCND1	9	2.14

Table 1: Co-mutation of METexon14 skipping events (N =440 skipping positive patients). METexon14 skipping events detected by WTS platform. Biomarkers with counts ≥ 5 were displayed. Co-mutations ≥ 2% were displayed.

Protein Change	D1028H	D1028N	c.3082+2T>C	D1028Y	c.3082+1G>A	c.3082+1G>T	c.3082+3A>T	c.3082+1delG	c.3082+2T>A	c.3082+3A>G	c.3082+1G>C
N	37	31	25	23	20	20	13	10	9	9	8
NGS-MET	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)	88.57	83.87	79.17	86.36	94.74	90.00	66.67	100.00	100.00	44.44	100.00
NGS-TP53	45.71	37.93	28.00	50.00	55.56	21.05	53.85	40.00	33.33	44.44	42.86
CNA-MDM2	25.71	9.68	37.50	13.64	10.00	21.05	15.38	10.00	0.00	0.00	12.50
CNA-HMGA2	23.33	11.11	19.05	22.22	5.56	18.75	18.18	0.00	0.00	0.00	12.50
CNA-CDK4	14.29	0.00	12.00	13.64	15.00	10.00	7.69	10.00	0.00	0.00	0.00
TMB-High	10.81	6.45	8.00	8.70	0.00	5.26	0.00	11.11	0.00	22.22	25.00
NGS-RB1	3.57	5.26	6.67	0.00	6.67	0.00	28.57	0.00	0.00	0.00	0.00
CNA-WIF1	5.56	0.00	0.00	20.00	0.00	0.00	33.33	0.00	0.00		33.33
NGS-HRR	5.88	13.33	5.88	11.11	12.50	0.00	0.00	20.00	20.00	0.00	0.00
CNA-LGR5	0.00	0.00	0.00	0.00	0.00	16.67	0.00	0.00	0.00		33.33
NGS-NF1	8.70	0.00	5.88	0.00	0.00	8.33	0.00	12.50	0.00	11.11	0.00
NGS-POT1	2.78	3.45	8.00	4.55	5.00	10.00	7.69	0.00	0.00	0.00	25.00
NGS-PIK3CA	2.70	0.00	4.00	8.70	5.00	0.00	7.69	11.11	0.00	0.00	12.50
NGS-BRCA2	2.86	3.23	4.00	4.35	0.00	5.00	0.00	0.00	0.00	0.00	0.00
NGS-SMAD4	2.70	3.23	4.00	0.00	0.00	0.00	7.69	0.00	12.50	0.00	12.50
CNA-LRIG3	0.00	0.00	0.00	8.33	0.00	0.00	0.00	0.00	0.00		33.33
NGS-ARID1A	0.00	0.00	5.88	10.00	0.00	0.00	10.00	0.00	0.00	11.11	0.00
CNA-FGF3	9.38	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
CNA-FGF4	5.88	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
NGS-ARID2	2.86	3.33	0.00	4.55	0.00	0.00	0.00	0.00	0.00	0.00	25.00
CNA-FGF19	2.86	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
CNA-MET	2.86	3.23	4.00	0.00	5.00	0.00	0.00	10.00	0.00	11.11	0.00
NGS-CDKN2A	2.78	3.23	0.00	0.00	0.00	5.26	0.00	0.00	0.00	0.00	0.00
NGS-CHEK2	5.56	3.33	0.00	0.00	5.00	0.00	0.00	0.00	12.50	0.00	0.00
CNA-CCND1	2.86	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00

Table 2: For all MET skipping events led by MET mutations, protein change information was gathered using WES platform. Protein change groups with sample size ≥ 5 were displayed.

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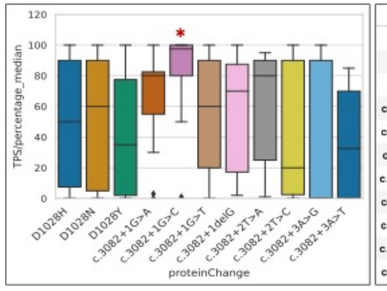
Results

Among all METex14 cases, 8.6% were TMB-high, but this varied by specific mutation with a median TMB of 2 mt/Mb in MET c.3082+2T>A and a median of 7 mt/Mb in MET c.3082+1G>C (q<0.05).



	counts	TPS_median
D1028H	35	50.0
D1028N	31	60.0
D1028Y	22	35.0
c.3082+1G>A	19	80.0
c.3082+1G>C	8	97.5
c.3082+1G>T	20	60.0
c.3082+1delG	10	70.0
c.3082+2T>A	9	80.0
c.3082+2T>C	24	20.0
c.3082+3A>G	9	0.0
c.3082+3A>T	12	32.5

Figure 1: PD-L1 TPS score evaluation, utilizing the 22C3 clone. The c.3082 + 1G>C group displayed the highest median TPS score whereas c.3082 + 3A>G group displayed the lowest median TPS score.

PD-L1 expression ≥ 1% was present in 82.2% of METex14 samples but also varied by specific METex14 mutation with a median PD-L1 tumor proportion score (TPS) of 97.5% in MET c.3082+1G>C and a median TPS of 0% in MET c.3082+3A>G (q<0.05).

Co-mutations varied by histology: in squamous METex14, 90.4% had TP53 mt (p<0.001), 17.9% had KMT2D mt (p<0.05), and 10.7% had PIK3CA mt (p<0.05), while in non-squamous METex14, 60.7% had TP53 mt, 2.7% had KMT2D mt, and 4.3% had PIK3CA mt.

Features	Squamous	Non-Squamous
NGS-TP53	90.40	60.70
NGS-KMT2D	17.87	2.72
NGS-POT1	0.89	1.53
NGS-PIK3CA	10.70	4.31
CNA-TLX1	0.51	0.47
CNA-MDM2	0.87	2.09
NGS-SMAD4	2.08	2.77

Table 3: Co-mutation variation by squamous and non-squamous histology.

Survival was numerically shorter in squamous METex14 NSCLC compared to non-squamous (HR 1.22, p=0.47, mOS 336 vs.1106 days).

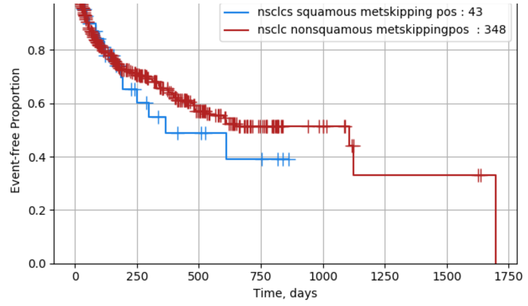


Figure 2: Kaplan Meier Curve displaying shorter survival in squamous METex14 NSCLC compare to non-squamous (HR 1.22, p=0.47, mOS 336 vs.1106 days).

Conclusions

There is significant heterogeneity within METex14 NSCLC with differences in co-mutations, TMB, and PD-L1 expression noted among different METex14 mutations. While METex14 is detected in both squamous and non-squamous NSCLC, there are differences in enrichment of oncogenic pathways. The clinical impact of these differences warrants further investigation.