Genomic comparison of MET exon 14 skipping and MET amplified non-small cell lung cancer

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INTRODUCTION

In non-small cell lung cancer (NSCLC), the *MET* tyrosine kinase receptor can be dysregulated by mutations and/or gene amplification. The most common *MET* mutation is in exon 14 (METex14), leading to impaired receptor degradation and increased *MET*-mediated signaling causing sustained tumor proliferation. *MET* amplification also leads to continued *MET* signaling and oncogenesis and can be a mechanism of resistance to targeted therapy. We sought to compare the genomic landscape of METex14 and high-level *MET* amplified tumors, both of which can be targeted with tyrosine kinase inhibitors.

METHODS

Tumor mutation burden (TMB), neoantigen load, PDL1, and the proportion of immune cell subtypes were evaluated from patient derived genomic profiles of NSCLC. PDL1 status was determined by IHC. Differences between groups were assessed by Chi-squared/Fisher's Exact tests or Kruskal-Wallis tests. Prevalence of gene alterations was compared with false-discovery correction for multiple testing. Analyses were two-sided with statistical significance evaluated at the 0.05 alpha level or 0.05 q level.

Characteristic	Overall, N = 18,047[1]	MET Exon 14 mutation, N = 276[1]	MET Amplification, N = 138[1]	MET other mutations, N = 27[1]	MET WT, N = 17,606[1]	p-value[2]
Age at Diagnosis						<0.001
Median (IQR)	68 (61, 75)	76 (70, 81)	66 (59, 73)	77 (67, 82)	68 (61, 75)	
Range	0, 90	48, 90	40, 87	46, 89	0, 90	
Unknown	243	14	2	0	227	
Gender						<0.001
Male	9,034 (50%)	110 (40%)	78 (57%)	18 (67%)	8,828 (50%)	
Female	9,013 (50%)	166 (60%)	60 (43%)	9 (33%)	8,778 (50%)	
Race						
White	9,678 (79%)	154 (81%)	71 (80%)	15 (75%)	9,438 (79%)	
Black or African American	1,478 (12%)	20 (11%)	10 (11%)	3 (15%)	1,445 (12%)	
Asian	509 (4.2%)	10 (5.3%)	6 (6.7%)	1 (5.0%)	492 (4.1%)	
Other Race	466 (3.8%)	5 (2.6%)	2 (2.2%)	1 (5.0%)	458 (3.9%)	
American Indian or Alaska Native	42 (0.3%)	0 (0%)	0 (0%)	0 (0%)	42 (0.4%)	
Native Hawaiian or Other Pacific Islander	13 (0.1%)	0 (0%)	0 (0%)	0 (0%)	13 (0.1%)	
Unknown	5,861	87	49	7	5,718	
Race						
White	9,678 (79%)	154 (81%)	71 (80%)	15 (75%)	9,438 (79%)	
Black or African American	1,478 (12%)	20 (11%)	10 (11%)	3 (15%)	1,445 (12%)	
Other	521 (4.3%)	5 (2.6%)	2 (2.2%)	1 (5.0%)	513 (4.3%)	
Asian	509 (4.2%)	10 (5.3%)	6 (6.7%)	1 (5.0%)	492 (4.1%)	
Unknown	5,861	87	49	7	5,718	
Ethnicity						0.9
Not Hispanic or Latino	7,091 (94%)	113 (96%)	50 (96%)	12 (100%)	6,916 (94%)	
Hispanic or Latino	449 (6.0%)	5 (4.2%)	2 (3.8%)	0 (0%)	442 (6.0%)	
Unknown	10,507	158	86	15	10,248	
Smoker status						<0.001
Current/former smoker	13,641 (85%)	160 (64%)	105 (85%)	23 (92%)	13,353 (85%)	
Never smoker	2,434 (15%)	89 (36%)	18 (15%)	2 (8.0%)	2,325 (15%)	
Unknown	1,972	27	15	2	1,928	

[1]n (%), [2]Kruskal-Wallis rank sum test; Pearson's Chi-squared test; Fisher's exact test

Table 1. Comprehensive genomic profiles from 18,047 NSCLC tumors were queried for METex14 mutations and high *MET* amplification defined as copy number gain (CNG) ≥10.

SUMMARY

- METex14 tumors exhibited differences in IO biomarkers and the somatic landscape compared to non-METex14 NSCLC tumors
- Variation in immune profiles may affect immunotherapy selection in *MET*-altered NSCLC and require further exploration

RESULTS

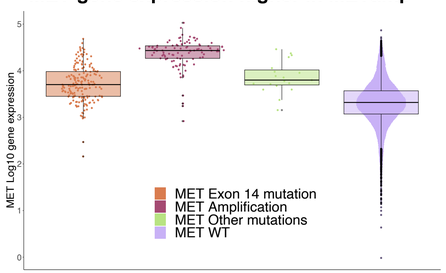

Figure 1 - Overall *MET* RNA expression in the full NSCLC cohort. METamp showed higher MET expression compared to METex14 (p< 0.001).

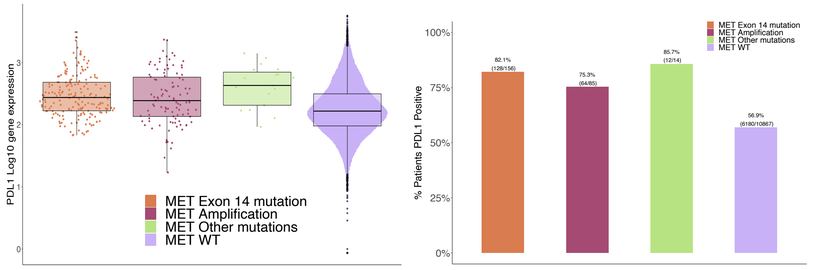

Figure 2 - *PDL1* gene expression and PDL1 IHC expression is highest in METex14 compared to METamp (p < 0.001). PDL1 IHC positivity was 82% in METex14 compared to 75% in METamp and 57% in METwt

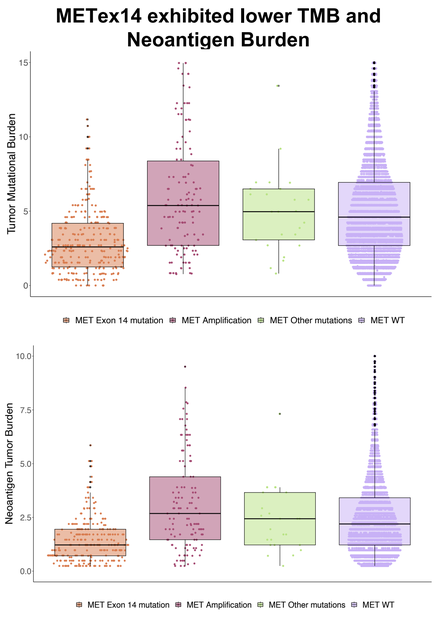

Figure 3 - Comparison of overall median TMB expression and overall neoantigen burden. Compared to METamp, METex14 exhibited lower TMB (p < 0.001) and neoantigen burden (p < 0.001)

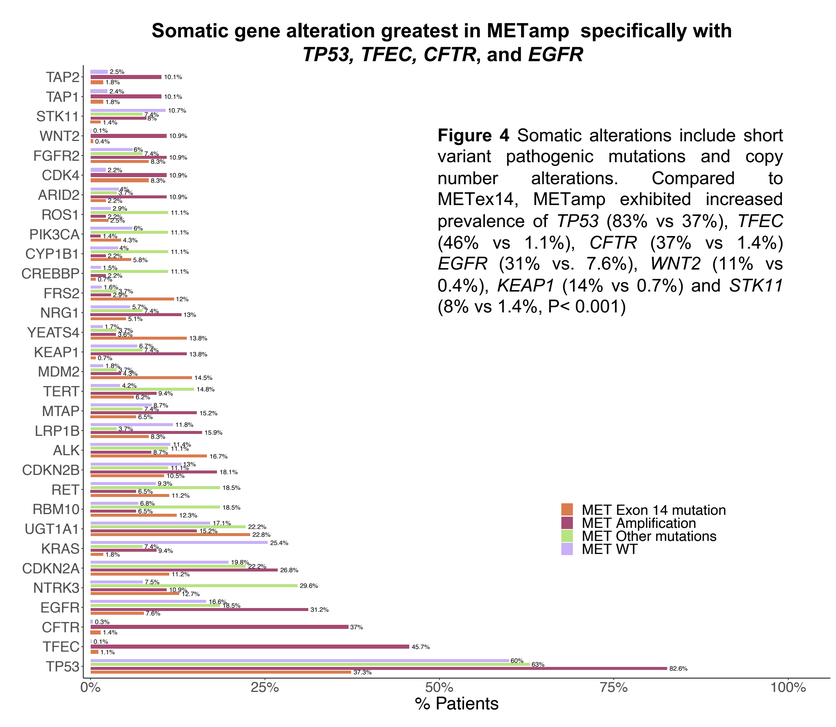

Figure 4 Somatic alterations include short variant pathogenic mutations and copy number alterations. Compared to METex14, METamp exhibited increased prevalence of *TP53* (83% vs 37%), *TFEC* (46% vs 1.1%), *CFTR* (37% vs 1.4%) *EGFR* (31% vs. 7.6%), *WNT2* (11% vs 0.4%), *KEAP1* (14% vs 0.7%) and *STK11* (8% vs 1.4%, P< 0.001)

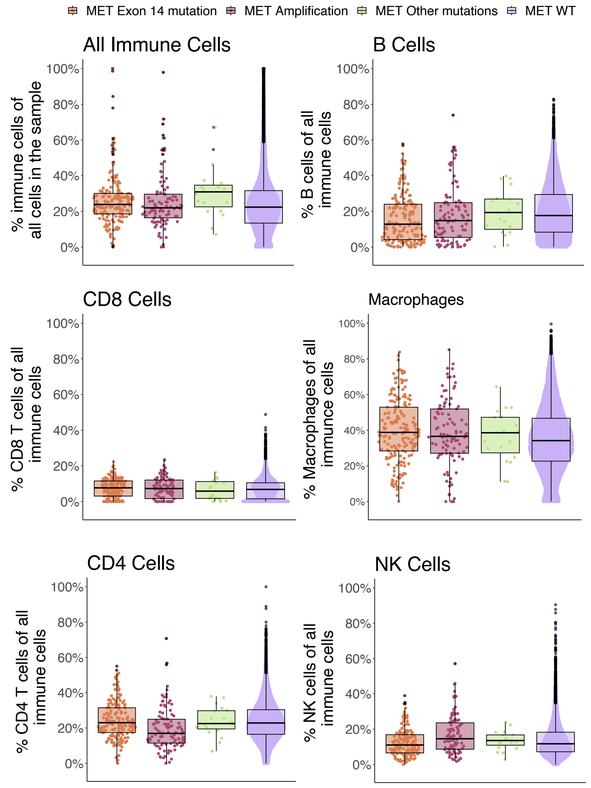

Figure 5. Compared to METex14, METamp %CD4 T cells were lower (p< 0.001) and %NK cells were higher (p< 0.001)

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