Characterization of *MET*exon14 skipping alterations (*MET*ex14) in non-small cell lung cancer (NSCLC) using whole transcriptome sequencing (WTS)

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Abstract #9122/Poster #108

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Background:

- DNA alterations in exon 14 splice sites result in increased MET stability and oncogenesis in NSCLC
- Effects of these alterations on transcriptome-level have not yet been fully characterized
- We present the largest cohort study of *MET*ex14 using WTS and identify potential actionable therapeutic targets

Methods:

- 21,582 NSCLC tumor samples underwent genomic profiling at Caris Life Sciences
- *MET*ex14 were captured by WTS and MET RNA expression quantified
- Inflammatory gene signatures were quantified using prior established immunogenic signatures (Ayers 2017, Spranger 2016) and QuanTiSeq
- ssGSEA analysis was used to evaluate pathway enrichment

Results:

Table 1. Baseline clinicopathologic characteristics

Baseline characteristics	*MET*ex14 (N, %)	WT (N, %)	p-value
	N=533	N= 21,049	
Male	231 (43.3)	10,669 (50.7)	<0.05
Female	302 (56.7)	10,380 (49.3)	
Never smoker	14/104 (13.5)	236/6107 (3.9)	<0.0001
Light smoker (<15 pack-year)	83/104 (79.8)	3989/6107 (65.3)	
Current heavy smoker	7/104 (6.7)	1882/6107 (30.8)	
Age, median	77 (41-90)	69 (21-90)	<0.0001
Histology			
Adenocarcinoma	324 (60.8)	12,423 (59.0)	<0.001
Squamous	57 (10.7)	4,849 (23.0)	
Adenosquamous	15 (2.8)	181 (0.9)	
Sarcomatoid	21 (3.9)	181 (0.9)	
Large cell	1 (0.2)	56 (0.3)	
others	115 (21.6)	3359 (16)	

***MET*ex14 were enriched in female gender, older age, light smokers, and sarcomatoid histologies**

Figure 1A. Spatial representation of *MET*ex14 mutation subtypes

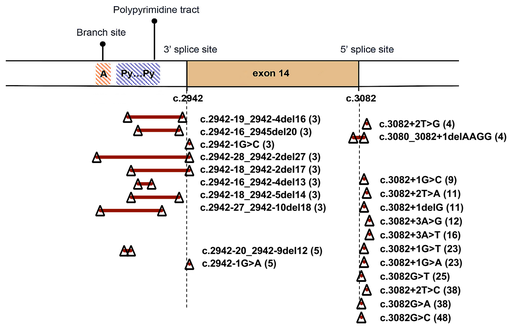
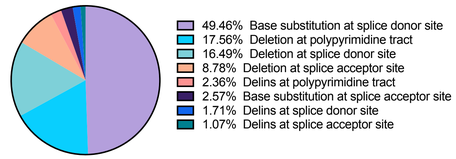
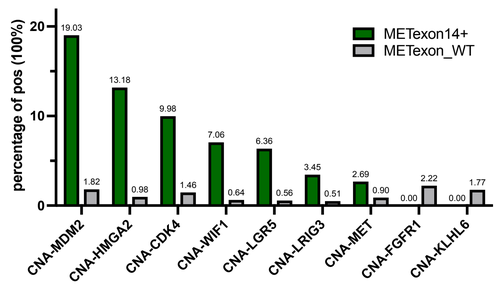


Figure 1B. Distribution of *MET*ex14 mutation subtypes



The most common mutation subtype was base substitution at the donor splice site (5' splice site of intron 14).

Figure 2. Co-alterations in *MET*ex14 and *MET* WT

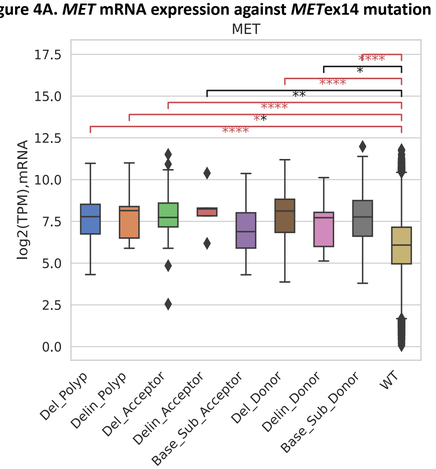


The most commo co-alterations were *MDM2*, *HMGA2*, and *CDK4*, co-localizing to chromosome 12q13-15.

Figure 3. Ratios of *MET*ex14 mutation junction reads to WT junction reads in *MET*ex14/Amp+ (CNA ≥ 6) vs. *MET*ex14/Amp-

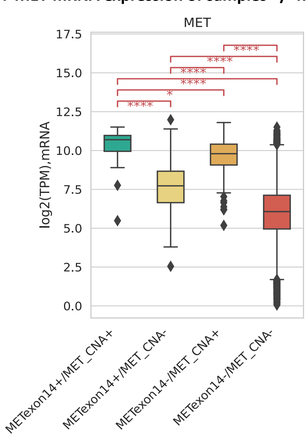
The *MET* skipping variant was preferentially expressed in *MET* co-amplified samples.

Figure 4A. *MET* mRNA expression against *MET*ex14 mutation subtypes



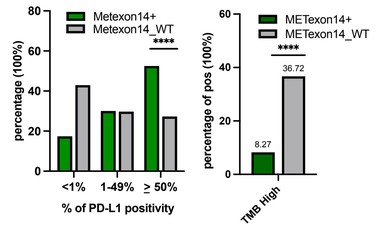
Most mutation subtypes resulted in 3-fold increase in *MET* mRNA expression compared to WT.

Figure 4B. *MET* mRNA expression of samples +/- *MET* co-amplification



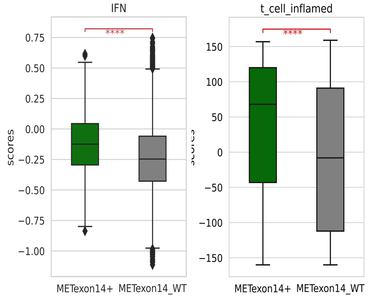
***MET* co-amplification (CNA ≥ 6) resulted in 24-fold increase in *MET* expression compared to 13-fold increase in *MET* amplification alone and 3-fold increase in *MET*ex14 alone compared to WT.**

Figure 5. PD-L1 and TMB distribution



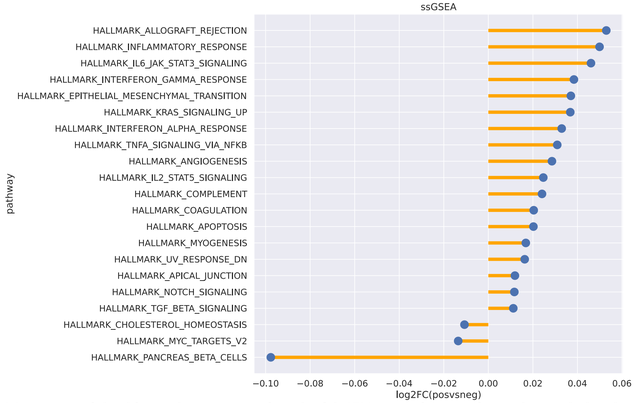
***MET*ex14 were enriched in high PD-L1 expression (PD-L1 ≥ 50), but had lower frequency of patients with high TMB (≥10 mut/Mb) compared to *MET* WT, with median TMB 8 mut/Mb for *MET*ex14 and 37 mut/Mb for *MET* WT.**

Figure 6. IFN-γ signatures and T-cell inflammation signature in *MET*ex14 and *MET* WT



***MET*ex14 were enriched in gene signatures associated with IFN-γ and T-cell inflammation.**

Figure 7. ssGSEA pathway analysis of *MET*ex14 patients.



***MET*ex14 were enriched in pathways associated with IFN-γ, angiogenesis, and cytoskeletal remodeling.**

Conclusions:

- Co-alterations were common with *MDM2* (12q15), *HMGA2* (12q14.3), and *CDK4* (12q14.1) in *MET*ex14
- Co-amplification of *MET* resulted in synergistic increase in *MET* expression
- *MET*ex14 were enriched in both immunogenic and immunosuppressive checkpoint signatures
- *MET*ex14 were associated with pathways associated with IFN-γ, cytoskeletal remodeling, and angiogenesis
- *MDM2*, *CDK4*, and angiogenic pathways may be key potential therapeutic targets in *MET*ex14 NSCLC