Genomic characterization of sporadic *MET*-amplified non-small cell lung cancer (NSCLC) and association with real-world outcomes

Ryan D. Gentzler[1], Nitya Sharma[2], Akash Mitra[2], Rotem Ben-Shachar[2], Michelle M. Stein[2], Justin Guinney[2], Halla Nimeiri[2], Wade Iams[3], Charu Aggarwal[4], and Jyoti Patel[4]

[1]University of Virginia Health, Charlottesville, VA | [2]Tempus Labs, Inc., Chicago, IL | [3]Division of Hematology/Oncology, Vanderbilt University, Nashville, TN | [4]University of Pennsylvania, Abramson Cancer Center, Philadelphia, PA
[5]Feinberg School of Medicine, Northwestern University, Chicago, IL | **Correspondence:** Dr. Ryan D. Gentzler, RG2UC@virginia.edu

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INTRODUCTION

MET copy-number amplifications (CNAs) are implicated as a resistance mechanism in NSCLC patients treated with *EGFR*-targeted tyrosine kinase (TKI) inhibitors and are associated with poor outcomes. However, data are limited on sporadic MET CNAs — defined as existing genomic alterations preceding first-line (1L) TKI therapy — and their associations with known predictive immune biomarkers and clinical outcomes. This is the first real-world dataset to assess the prevalence of sporadic *MET* amplifications in NSCLC and their association with real-world clinical outcomes.

METHODS

We analyzed a de-identified, multimodal dataset of 3,998 NSCLC patients biopsied prior to or within 30 days of the start of 1L therapy. Tempus xT is a targeted DNA panel that detects single-nucleotide variants (SNVs), insertions and/or deletions (indels), and copy number variants. *MET* CNAs were identified as follows: ≥ 4 copies <8 copies (CN-intermediate); ≥8 copies (CN-high). The combined high + intermediate cohort was compared to patients that were copy-number neutral (CN-N, 2 copies). Patients with *MET* exon 14-skipping mutations were excluded.

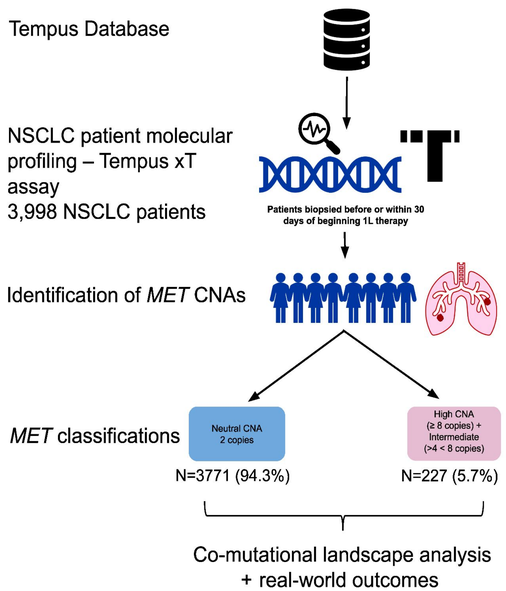

Figure 1. General workflow

SUMMARY

- High (H; ≥ 8 copies) + intermediate (I; ≥ 4 and < 8 copies) sporadic *MET* CNAs represent a unique genomic subset (5.7% TKI-naïve NSCLC patients) with distinct biology: 18% co-occur with *EGFR* mutations and 12% co-occur with *KRAS* G12C
- Patients with sporadic H+I *MET* CNAs had higher PD-L1 and high TMB, both positive predictive biomarkers of immune checkpoint inhibitor (ICI) therapy and trend toward better rwOS when treated with 1L ICI-based therapy
- Our real-world analysis suggests that combination therapy with ICI should be considered for future clinical trials evaluating this *EGFR* wild-type subset of sporadic *MET* CNA

RESULTS

Cohort Demographics and Clinical Characteristics

Patient Characteristic	High + Intermediate N = 227[1]	Neutral N = 3771[1]	p-value[2]
Gender			0.3
Female	100 (44%)	1,797 (48%)	
Male	127 (56%)	1,974 (52%)	
Age at Diagnosis	67 (60, 73)	68 (61, 75)	
Unknown	3	22	
Race			0.7
White	145 (77%)	2,357 (79%)	
Black or African American	23 (12%)	329 (11%)	
Other	10 (5.3%)	141 (4.7%)	
Asian	8 (4.3%)	104 (3.5%)	
Native Hawaiian or other Pacific Islander	0 (0%)	4 (0.1%)	
Not stated	1 (0.5%)	10 (0.3%)	
American Indian or Alaska Native	1 (0.5%)	6 (0.2%)	
Unknown	39	820	
Diagnosis			
Lung adenocarcinoma	185 (84%)	2,575 (71%)	<0.001
Lung squamous cell carcinoma	35 (16%)	1,048 (29%)	
Unknown	7	148	

[1]n (%); Median (IQR)
[2]Pearson's Chi-squared test; Wilcoxon rank sum test; Fisher's exact test

Table 1. Demographic information for all patients included in this study

First-line (1L) treatment status

	All Patients (n)	*MET* High + Intermediate (n)	*MET* Neutral (n)
Full cohort	3998	227	3771
Treated with ICI +/- chemo	1672	94	1578

Table 2. Patient treatment status was assessed before or within 30 days of starting 1L therapy.

Prevalence of *EGFR* mutations stratified by *MET* copy number status

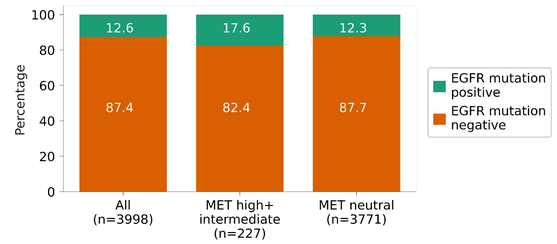

Figure 2. The majority of NSCLC patients in this data set do not harbor *EGFR* mutations. However, patients with high and intermediate *MET* CNAs are more likely to harbor *EGFR* mutations (n= 40/227, Fisher's exact p=0.02). Further results are restricted to *EGFR* wild-type samples.

Immunotherapy-related biomarkers and association with *MET* CNAs in *EGFR* wild-type NSCLC patients

Biomarker	*MET* High + Intermediate (N=187)	*MET* neutral (N=3307)	p-value
KRAS G12C+	20 (11%)	400 (12%)	0.64
STK11+	6 (3.2%)	432 (13%)	1.12E-05
KEAP1+	27 (14%)	275(8.3%)	0.007
TMB-H	40 (21%)	446 (13%)	0.004
PD-L1 Positive (≥50% TPS)	45 (45%*)	551 (26%*)	6.62E-05

*PD-L1 IHC was available for a subset of EGFR-mutation negative patients: n=100 MET high+intermediate and n=2130 MET neutral.

Table 3. Among *EGFR* wild-type patients, immunotherapy-related biomarkers are more prevalent in patients harboring *MET* CNAs, including PD-L1 positivity and TMB-High. *STK11* and *KEAP1* mutational prevalence similarly differ according to *MET* amplification status.

Presenting Author Declaration of Interest: Dr. Gentzler's travel and expenses have been compensated by Tempus. His full COI can be found in the abstract booklet.

TMB and PD-L1 TPS are significantly higher in *EGFR* wild-type, *MET* CNA NSCLC patients

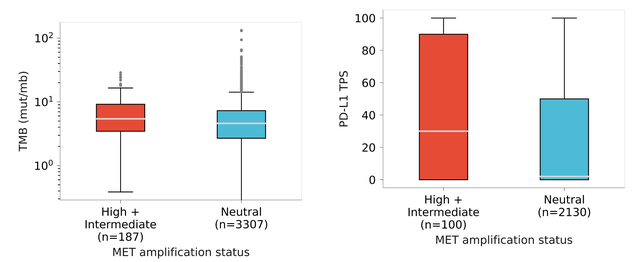

Figure 3. Tumor mutational burden (TMB, mut/MB; left) and PD-L1 Tumor Proportion Score (TPS; right) for *EGFR*-mutation negative samples, stratified according to sample MET CNA status. Table 3 shows binary classifications for TMB-High and PD-L1 positivity, including statistics.

Overall survival for *EGFR*- NSCLC patients with sporadic H+I *MET* CNAs receiving 1L ICI therapy

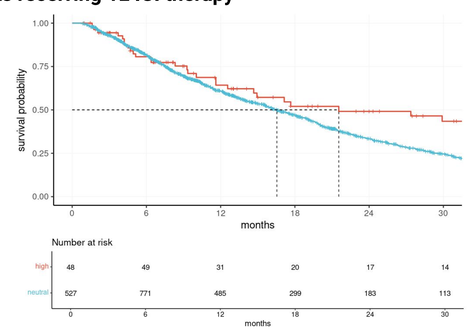

Figure 4. *EGFR*- NSCLC patients with sporadic H+I *MET* CNAs (median rwOS:21.5 months) trended towards improved survival compared to *EGFR* wild-type, *MET* neutral patients (median rwOS:16.5 months) on 1L ICI therapy (HR=0.81. p=0.22 [95% CI: 0.57-1.14]).

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