Molecular Characterization of *NF1*-mutated NSCLC and Clinical Outcomes

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Abstract

Background: NF1 is a tumor suppressor gene that regulates the RAS-MAPK and mTOR pathways. Co-mutations previously observed with *NF1*-mutations (mt) include *TP53*, *KRAS*, *EGFR* and rarely *HER2*, *STK11*, and *PIK3CA* mutations. We report a comprehensive molecular characterization with clinical outcomes analyses for *NF1*-mt non-small cell lung cancer (NSCLC).

Methods: Next-generation sequencing (NGS) of DNA (592-gene or whole exome) and RNA (whole transcriptome) was performed for NSCLC patient (pt) samples (n = 10,310) submitted to a CLIA-certified laboratory (Caris Life Sciences, Phoenix, AZ). RAS-MAPK and PI3K-AKT-MTOR signaling were assessed by transcriptional signatures of pathway activation (MAPK pathway Activation Score [MPAS], Wagle, 2018; and GSEA Hallmarks collection, respectively). PD-L1 by immunohistochemistry (IHC, positive: TPS ≥1%), high tumor mutational burden (TMB) defined as ≥10 mut/Mb, and deficient mismatch repair/high microsatellite instability (dMMR/MSI-High) was assessed by IHC/NGS. Overall survival (OS) was obtained from insurance claims. Statistical significance was determined using Chi-square & Wilcoxon rank sum tests. Q-values indicate P-values adjusted for multiple hypothesis testing (Benjamini-Hochberg).

Results: *NF1*-mt were identified in 1,045 NSCLC samples (10.1%). Concurrent *KRAS*, *EGFR*, *ERBB2*, *BRAF* or *MET* alterations are noted in Table 1, with no *ROS1*, *RET* or *ALK* fusions identified. Compared to *NF1*-wt, *NF1*-mt NSCLC was associated with increased RAS-MAPK expression (3.0-fold, P < 0.0001), while PI3K-AKT-MTOR-signaling was not significantly increased (2.1-fold, P = 0.12). Rates of TMB-High (51.7% vs 32.5%, P < 0.0001), PD-L1+ (69.1% vs 58.8%, P = 0.06), and dMMR/MSI-High (1.7 vs 0.7%, P < 0.05) were higher in *NF1*-mt samples. OS and duration on treatment from the start of Pembrolizumab (HR: 1.0 and 1.0, respectively) or other IOs (HR: 0.9 and 1.0, respectively) were not significantly different between *NF1*-mt and *NF1*-wt patients. However, among *NF1*-mt samples, high TMB and *TP53*-wt were associated with better OS (HR 0.6, P < 0.05 each).

Conclusions: *NF1*-mt patients rarely harbored actionable NSCLC driver co-alterations. *NF1*-mt cases showed increased activation of RAS-MAPK axis, which may represent a potential pathway to target with MEK inhibitors. *NF1*-mt are responsive to immunotherapy and better outcomes are seen with high TMB and absence of TP53 mutations. Further work is warranted to determine the influence of actionable drivers on targeted therapy outcomes in *NF1*-mt NSCLC.

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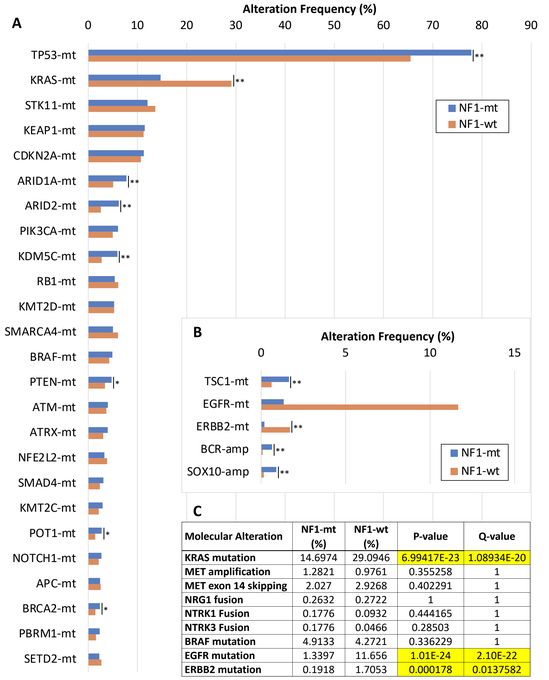
Results

Table 1 – Cohort demographics for *NF1*-mutated (mt) and *NF1*-wild type (wt) subgroups

- NF1 mutations identified in 1045 (10.1%) NSCLC patient tumors

Characteristic	*NF1*-mt	*NF1*-wt
Count, N (%)	1045 (10.1%)	9265 (89.9%)
Median Age, years (range)	70.0 (37 – 90+)	68.0 (0 – 90+)
Male, N (%)	524 (50.1%)	4655 (50.2%)
Female, N (%)	521 (49.9%)	4610 (49.8%)

Figure 1. Genomic alterations associated with *NF1*-mt NSCLC
(A) Alterations observed in ≥ 2% of *NF1*-mt samples. (B) Select alterations observed in < 2% of *NF1*-mt samples. (C) Summary of clinically relevant co-alterations.
mt = mutation, amp = copy number amplification (≥ 6 copies), *P<0.05, **Q<0.05.



C

Molecular Alteration	NF1-mt (%)	NF1-wt (%)	P-value	Q-value
KRAS mutation	14.6974	29.0946	6.99417E-23	1.08934E-20
MET amplification	1.2821	0.9761	0.355258	1
MET exon 14 skipping	2.027	2.9268	0.402291	1
NRG1 fusion	0.2632	0.2722	1	1
NTRK1 Fusion	0.1776	0.0932	0.444165	1
NTRK3 Fusion	0.1776	0.0466	0.28503	1
BRAF mutation	4.9133	4.2721	0.336229	1
EGFR mutation	1.3397	11.656	1.01E-24	2.10E-22
ERBB2 mutation	0.1918	1.7053	0.000178	0.0137582

Figure 2 – Immunotherapy-related biomarkers in *NF1*-mt NSCLC
Rates of TMB High (≥10 mut/Mb), PD-L1+ (22c3, TPS ≥1%), and dMMR/MSI-High were increased in *NF1*-mt samples.

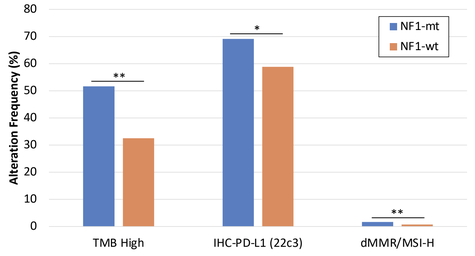


Figure 3 – Transcriptional profiling reveals increased RAS/MAPK pathway activation *NF1*-mt NSCLC.

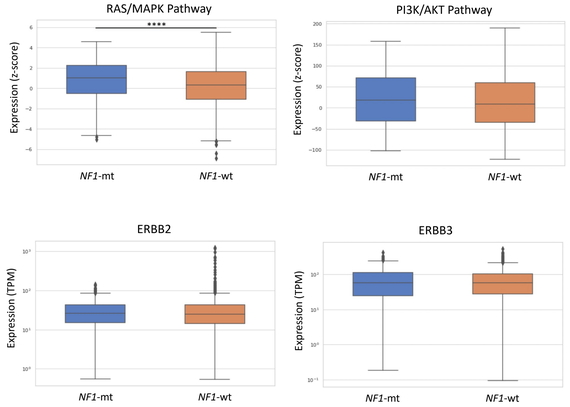
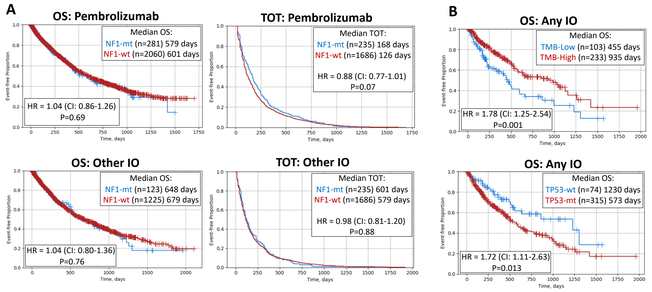


Figure 4 – Immunotherapy (IO)-related outcomes associated with NF1-mt patients
(A) Overall survival (OS) and time-on-treatment (TOT) from the start of Pembrolizumab or other IOs (atezolizumab, ipilimumab, or nivolumab). (B) OS from start of any IO for NF1-mt samples further stratified by TMB-High (≥10 mut/Mb) or TP53 mutation status.



Conclusions

- *NF1*-mt patients rarely harbored actionable NSCLC driver co-alterations.
- *NF1*-mt cases showed increased activation of RAS-MAPK axis, which may represent a potential pathway to target with MEK inhibitors.
- *NF1*-mt are responsive to immunotherapy and better outcomes are seen with high TMB and absence of TP53 mutations.
- Further work is warranted to determine the influence of actionable drivers on targeted therapy outcomes in *NF1*-mt NSCLC

References (or contact info)

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