Utilizing Molecular Profiling to Identify Potential Therapies in Sarcomatoid Lung Cancer

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Nothing to Disclose relevant to the abstract

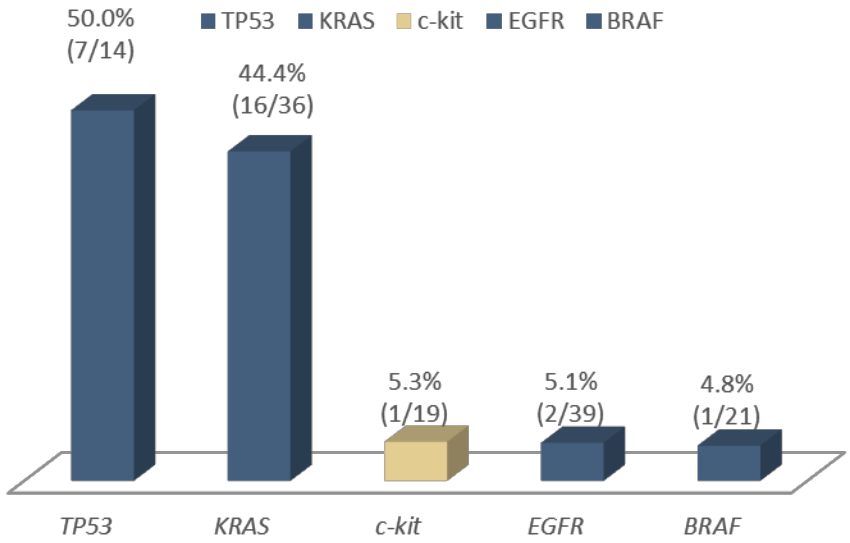
Background - sarcomatoid lung cancer (SLC)

- Comprises one percent of all lung malignancies.
- NSCLC with sarcoma-like differentiation or component of sarcoma.
- Five types per WHO: carcinosarcoma, giant cell, pleomorphic, pulmonary blastoma, spindle cell.
- NSCLC regimens and not sarcoma regimens (e.g. doxorubicin, ifosfamide) are typically utilized.
- Still, prognosis remains dismal. The purpose of this study, then, is to identify novel potential targets.

Methods – SLC cohort, multiplex testing

- A retrospective review of Caris' database (from 2003 to the present) identified 48 specimens diagnosed as sarcomatoid lung cancer (SLC).
- All diagnoses were confirmed by board-certified pathologists.
- Gene sequencing (Sanger or next-generation sequencing [Illumina TruSeq], up to 47 genes), immunohistochemistry (IHC), and *in situ* hybridization (FISH or CISH) were performed.
- The number of tests performed depended on tumor availability as well as what had been requested by the ordering physician.

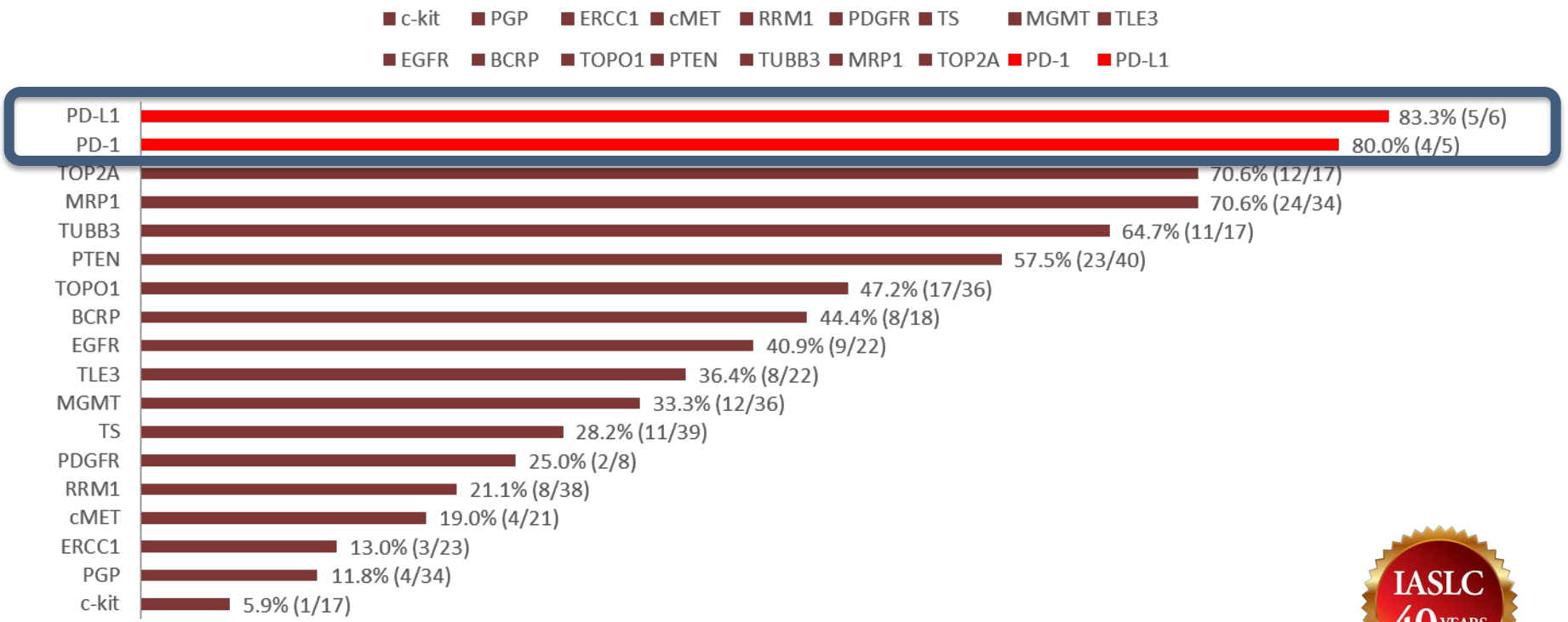
Results – Variants in SLC by NGS or Sanger



Distribution of NSCLC based on outside literature	
Gene	Frequency NSCLC
AKT1	1%
BRAF	1-3%
EGFR	10-35%
ERBB2	2-4%
KRAS	15-25%
NRAS	1%
PIK3CA	1-3%
PTEN	4-8%

- *Mutations (in **blue**) were considered shown were pathogenic (i.e. tumorigenic). The c-kit variant identified, H697N, was considered a variant of unknown significance or VUS (in **yellow**).*
- *The EGFR variants were L858R (x1) and exon20ins (x1). The specimen with EGFR L858R has co-occurring mutations in KIT (i.e. c-kit) and TP53.*
- *BRAF* variant detected was G469V at exon 11.
- *MET exon 14 alterations, reported as having a frequency of 22% in SLC, were not tested.*

Immunohistochemistry (IHC)



High PD-L1 Expression in SLC

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Sarcomatoid lung carcinomas show high levels of Programmed death Ligand-1 (PD-L1)

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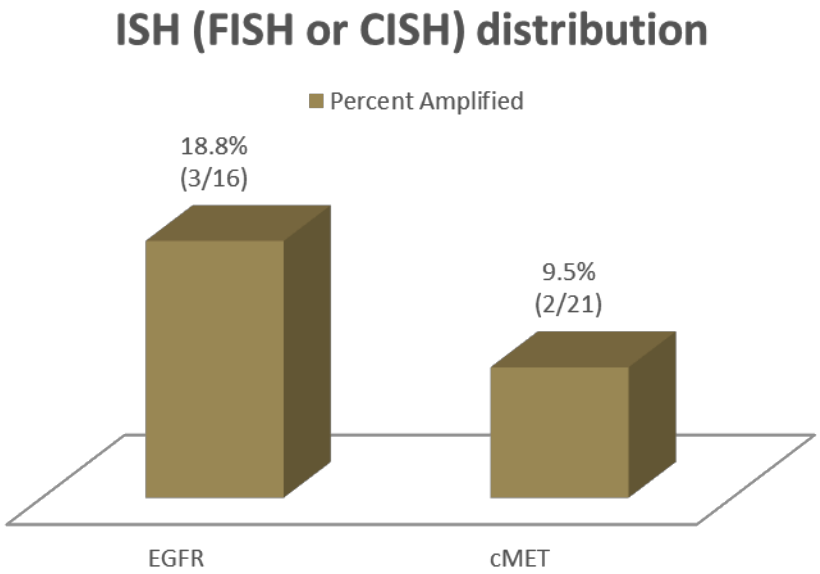
Abstract

Programmed death-1 (PD-1) is a co-inhibitory inducible receptor present on T-cells and macrophages. Tumor cells with increased programmed death ligand-1 (PD-L1) are believed to escape immunity through activation of PD-1/PD-L1 pathway and suppression of effector immune responses. Recent strategies targeting the PD-1/PD-L1 axis have shown promising results in patients with several tumors types, including lung carcinomas. Preliminary data suggests that PD-L1 protein expression might predictive response to such therapies. Sarcomatoid carcinomas (SCs) of the lung include rare subtypes of poorly differentiated non-small cell lung carcinomas (NSCLC) of high grade and aggressive behavior. The biology of these neoplasms is poorly understood and they frequently show increased local inflammatory and lymphocytic infiltration. Here, we report the expression of PD-L1 in 13 SCs from two large retrospective lung cancer cohorts. Using automated quantitative immunofloresence (aqIF/AQUA®) and a mouse monoclonal antibody directed against the extra-cellular domain of PD-L1, we show that 9 of 13 (69.2%) patients with SCs are positive for PD-L1 and their levels are higher than in conventional NSCLC. These results provide rationale for the potential use of targeted immunetherapy in lung SCs.

Results – in situ hybridization (ISH) in SLC



Distribution in NSCLC based on outside literature	
Gene	**Frequency in NSCLC**
ALK	3 – 7%
MET	2-4%
ROS1	1%

- *EGFR amplification may warrant further exploration. Amplification was independent of EGFR mutation.*
- *Presence of MET (i.e. cMET) gene is higher than what is reported in the literature.*
- *No ALK, ROS1 rearrangements or ERBB2 (HER2) amplification found.*

Conclusions

- PD-1 and PD-L1 are differentially expressed in sarcomatoid lung cancer, warranting clinical trials with checkpoint inhibitors.
- EGFR mutations were rare in this SLC cohort and its clinical significance merits investigation
- KRAS mutations are noticeably higher in this SLC cohort, consistent with a history of heavy or chronic smoking typically noticed in this disease.
- MET amplification warrants further exploration. In addition, although not reported, MET exon 14 splicing alterations merits further investigation.
- In all, our study provides a baseplate for clinical trials design. Further molecular analyses and clinical trials are urgently needed.