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Evaluation of the Genomic and Immune Profile of Patients with Lung Adenosquamous Carcinoma and Association of Response to Treatment

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ASCO Abstract# 8567

Background

- Adenosquamous carcinoma (LUAS) is an uncommon histology, accounting for 0.4-4% of lung cancer. [1]
- LUAS is defined by the WHO as a cancer containing both adenocarcinoma and squamous cell carcinoma components with at least 10% of both. [2]
- Intratumoral heterogeneity can impact the identification of gene alterations, and lead to diagnostic and treatment challenges. Patients with LUAS, compared to other lung cancer types, have worse prognosis and survival, with more distant metastases and local recurrences.[3]
- In this study, we evaluated the genomic alterations, PD-L1 status and clinical data of patients with lung adenosquamous cases and compared to patients with lung adenocarcinoma and squamous cell

Methods

- NSCLC samples (n = 35404) underwent NextGen Sequencing of DNA (592 genes or whole exome) and/or RNA (whole transcriptome) at Caris Life Sciences.
- PD-L1 expression was assessed using IHC (22c3; positive: TPS ≥1%).
- High tumor mutational burden (TMB-H) was defined as ≥10 mut/MB.
- Cell infiltration in the tumor microenvironment was estimated by quanTIseq.
- Gene expression profiles were analyzed for transcriptomic signatures (IFN-γ) predictive of IO response.
- Real-world overall survival (rwOS) was obtained from insurance claims data, calculated from time of biopsy to last contact. Time on treatment (TOT) was calculated from the first pembrolizumab (pembro) treatment to the last.
- Mann-Whitney U and X^2/Fisher-Exact tests were applied where appropriate, with *p*-values adjusted ($p < .05$).

Genomic Landscape of Lung Adenosquamous Tumor

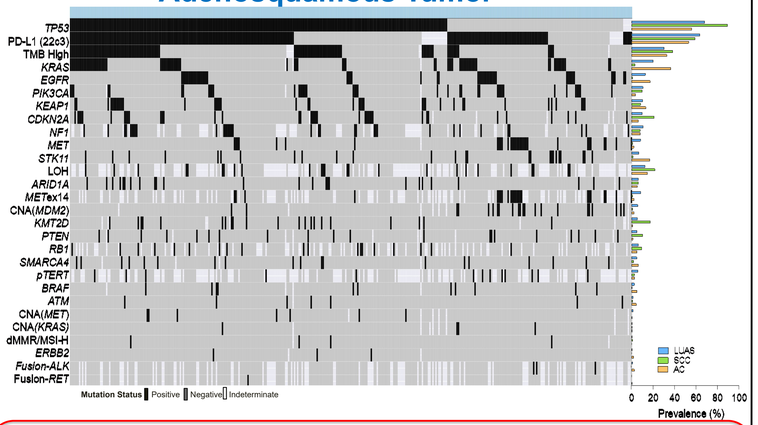
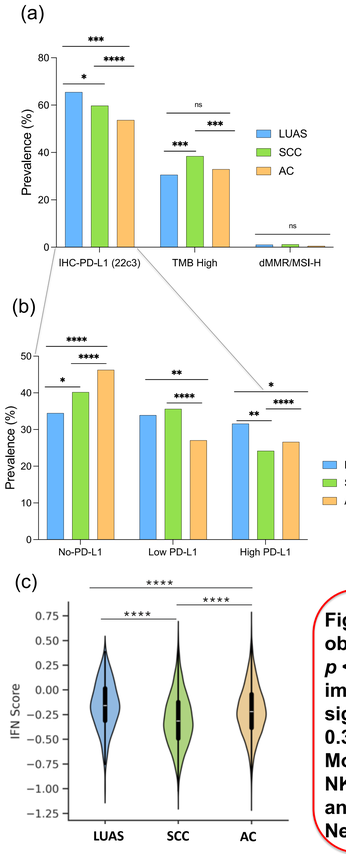


Figure 1: Genomic Landscape of Lung Adenosquamous. Among NSCLC samples, 1.0% (n=374) were LUAS, 26.5% (n = 9365) were squamous (SCC) and 72.5% (n = 25665) were adenocarcinoma (AC). LUAS exhibited actionable alterations in 29% (n = 110/374) of cases, with *MET* exon 14 skipping alteration (*METex14*) significantly higher in LUAS compared to SCC or AC (9.02% vs 1.21% vs 2.61%, $p < 0.01$).

Table 1: Targetable Alterations in of Lung Adenosquamous.

Targetable Alterations	LUAS	SCC	AC	P-value
KRAS (G12C)	8.63%	1.37%	13.24%	p<0.01
EGFR (Actionable) Exon19del Exon21 – L858R, Exon20Ins	12.10% 6.47% 3.50% 0.81%	0.93% 0.41% 0.35% 0.07%	14.70% 7.67% 5.09% 1.06%	p<0.01
*MET*ex14skip	9.02%	1.21%	2.61%	p<0.01
BRAF (V600E)	0.54%	0.13%	1.73%	p<0.01
ALK-Fusion	1.13%	0.12%	2.88%	p<0.01
RET-Fusion	0.38%	0.03%	1.06%	p<0.01

Intratumoral Microenvironment Composition and IO Response Markers



(d)

Median Immune cell infiltration in Lung Adenosquamous Carcinoma

Median Cell Fractions (%)	LUAS	SCC	AC
Neutrophils	5.57	5.23	4.85*
NK cells	2.68	2.49*	2.94*
T cells CD8	0.39	0.11*	0.27
Macrophages M2	6.08	4.65*	6.19
Macrophages M1	4.57	2.64*	5.12
B cells	4.08	4.19	3.87
Tregs	2.92	1.75*	2.76

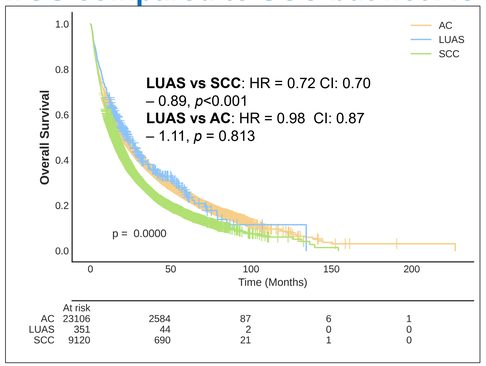
Immune Cells/ Gene Expression (Low Med High)

Median Immune Checkpoint Genes Expression

Genes	LUAS	SCC	AC
PDCD1LG2	1.45	1.32*	1.28*
PDCD1	0.82	0.71*	0.79
CTLA4	1.91	1.63*	1.64*
CD86	3.53	3.22*	3.48
IDO1	2.85	2.30*	2.24*
CD274	3.21	3.12*	3.03
CD80	2.89	2.57*	2.80*
HAVCR2	4.51	4.00*	4.50*
LAG3	1.04	1.04	0.86
IFNG	0.84	0.70	0.69

Figure 2: PD-L1+ positivity was significantly observed in LUAS (65.5% vs 59.8% vs 53.7%, p <0.01), along with elevated expression of immune checkpoint genes and the IFN-γ signature compared to AC and SCC (-0.16 vs -0.31 vs -0.22, arbitrary units, p < 0.001). Moreover, LUAS exhibited significantly higher NK cells, CD8 T cells, macrophages (M1/M2) and Tregs compared to SCC while it had more Neutrophils than AC.

LUAS is associated with prolonged rwOS compared to SCC but not AC



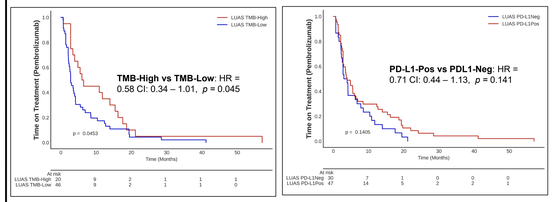


Figure 3: LUAS showed improved rwOS compared to SCC (HR 0.792, p<0.01), with no difference noted in the rwOS between LUAS and AC (HR = 0.98, p = 0.81). While PD-L1+ was not associated with TOT on pembrolizumab in LUAS, high TMB showed improved TOT on pembrolizumab in LUAS.

Summary

- **This study provides a comprehensive genomic landscape of LUAS, highlighting actionable alterations in ~ 29% of cases.**
- **LUAS exhibits distinct molecular and clinical features compared to AC and SCC, with enrichment in actionable *METex14*, emphasizing the need for NGS testing.**
- **Although PD-L1 status may not significantly impact TOT in LUAS, it remains relevant in other NSCLC subtypes on IO and high TMB emerges as a potential biomarker for favorable TOT on pembrolizumab in LUAS, warranting further investigation.**

References

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