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Complex Markers of Survival from Pembrolizumab: The Potential Predictive Role of Tumor Mutational Burden (TMB) and KRAS in Non-small Cell Lung Cancer

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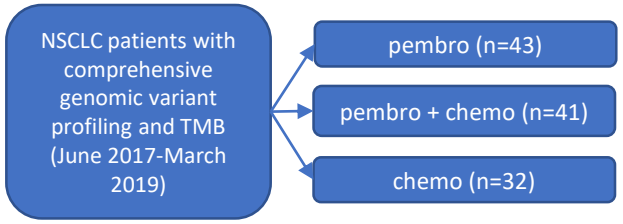
INTRODUCTION

Pembrolizumab, with or without chemotherapy, is NCCN guideline-recommended treatment for NSCLC cancer patients depending on tumor PD-L1 status by IHC. PD-L1 IHC provides guidance for treatment selection for response, but does not accurately predict survival benefit from pembrolizumab. Emerging evidence suggests TMB and other genomic markers (KRAS, STK11, TP53 mutations), may have clinical utility for predicting overall survival (OS) benefit [1-2].

METHODS

We identified EGFR/ALK wild-type NSCLC patients (n=116) whose tumors underwent comprehensive next generation sequencing (NGS) profiling for genomic variants and TMB, and PD-L1 IHC 22C3 testing prior to therapy selection. All testing was performed in a CAP and CLIA certified laboratory as part of standard care.

Figure 1. Patient Identification

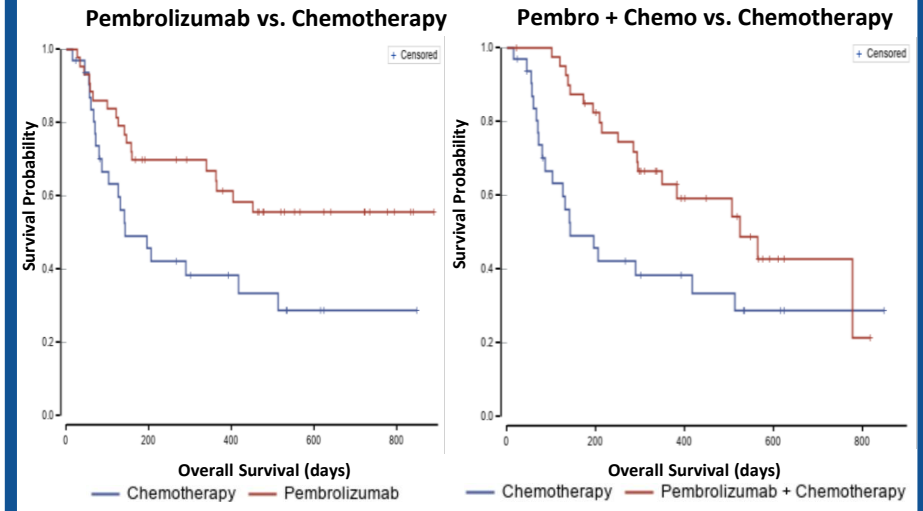


TMB was assessed using a 1.75 Mb capture of 409 oncogenes with full exon coverage (DNA-Seq), and TMB high status interpreted as ≥10 mutations/Mb. Electronic pharmacy records were curated to create comprehensive pre and post-test treatment histories for each patient.

Table 1. Patient Characteristics by Treatment Group

		Pembro (N=43)	Pembro + Chemo (N=41)	Chemo (N=32)	Total (N=116)
Age, mean years		69.3	63.9	68.6	67.1
Gender	Male	18 (41.9)	23 (56.1)	16 (50.0)	57 (49.1)
	Female	25 (58.1)	18 (43.9)	16 (50.0)	59 (50.9)
Histology	non-squamous	31 (72.1)	38 (92.7)	30 (93.8)	99 (85.3)
	squamous	12 (27.9)	3 (7.3)	2 (6.3)	17 (14.7)
Stage	metastatic	38 (88.4)	39 (95.1)	26 (81.3)	103 (88.8)
	unresectable	5 (11.6)	2 (4.9)	5 (15.6)	12 (10.3)
	early	0 (0.0)	0 (0.0)	1 (3.1)	1 (0.9)
Smoking history (Y)		38 (88.4)	38 (92.7)	29 (90.6)	105 (90.5)
ECOG	0	10 (23.3)	8 (19.5)	9 (28.1)	27 (23.3)
	1	28 (65.1)	26 (63.4)	19 (59.4)	73 (62.9)
	2	5 (11.6)	7 (17.1)	4 (12.5)	16 (13.8)
TMB ≥ 10mut/Mb (high)		22 (51.2)	19 (46.3)	14 (43.8)	55 (47.4)
PD-L1 IHC 22C3	≥ 50% (high)	37 (86.1)	10 (24.4)	7 (21.9)	54 (46.6)
	1-49% (low)	5 (11.6)	17 (41.5)	11 (34.4)	33 (28.4)
	0% (negative)	1 (2.3)	14 (34.2)	14 (43.8)	29 (25.0)
KRAS mutant		15 (34.9)	11 (25.8)	13 (40.6)	39 (33.6)
TP53 mutant		20 (48.8)	24 (55.8)	16 (50.0)	60 (51.7)
STK11 mutant		3 (6.98)	10 (24.4)	5 (15.6)	18 (15.5)
Treatment Line	1	27 (62.8)	26 (63.4)	25 (78.1)	78 (67.2)
	2	11 (25.6)	12 (29.3)	5 (15.6)	28 (24.1)
	>=3	5 (11.6)	3 (7.3)	2 (6.3)	10 (8.6)
Time on drug, median days		184	120	55	115

Figure 2. Overall Survival (OS) by Treatment Group



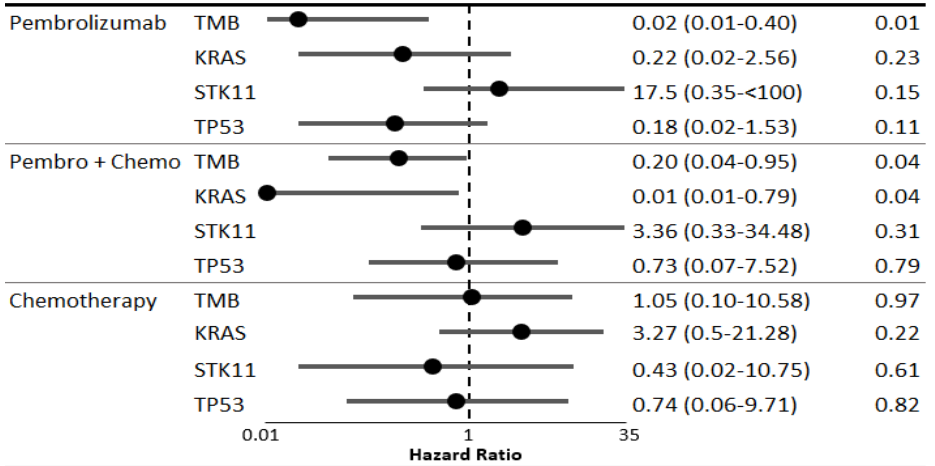
** Kaplan-Meier estimates of overall survival by treatment group.*

Table 2. Hazard Ratios by Treatment Group

Comparison	Hazard Ratio	Confidence Interval	P Value
Pembrolizumab vs. Chemotherapy	0.25	0.10 – 0.64	< 0.01
Pembro + Chemo vs. Chemotherapy	0.31	0.14 – 0.67	< 0.01
Pembrolizumab vs. Pembro + Chemo	0.81	0.34 – 1.95	0.81

- TMB, smoking, ECOG performance status identified as significant covariates.
- PD-L1 IHC status was not associated with OS for any treatment.

Figure 3. Hazard Ratios by Treatment Group and Marker Status



** Cox regression model to evaluate marker Hazard Ratio for each treatment group, controlling for potential covariates: age, sex, smoking comorbidity index, performance status, treatment line, prior treatment types, and co-occurring genomic alterations. No covariates were significant.*

- **TMB-high** status was associated with OS benefit with pembrolizumab monotherapy or in combination with chemotherapy.
- **KRAS mutant** status was significant for OS benefit from pembrolizumab + chemotherapy, but not pembrolizumab monotherapy or chemotherapy alone.
- **STK11 mutant** status showed a trend toward increased risk of death, whereas **TP53 mutant** status trended toward survival benefit.

CONCLUSIONS

- TMB has potential predictive power for determining overall survival benefit from pembrolizumab in NSCLC
- KRAS, STK11, and TP53 mutational status demonstrated potential prognostic relevance for NSCLC.

REFERENCES

1. Remon et al. PMID: 32179179
2. Skoulidis et al. PMID: 31406302