Smoking history as a potential predictor of Immune Checkpoint Inhibitor efficacy in metastatic non-small cell lung cancer

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Background

Despite the therapeutic efficacy of Immune Checkpoint Inhibitors (ICIs) in a subset of patients, consistent and easily obtainable predictors of efficacy remains elusive. We define the predictive impact of smoking history on the clinical outcomes of ICI monotherapy in metastatic NSCLC.

Methods

This study was conducted on 644 advanced NSCLC patients treated with ICI monotherapy between 04. 2013 and 09.2020 at DFCI and BWH. Patient smoking history, clinicopathological characteristics, Tumor Mutation Burden by clinical targeted Next Generation Sequencing, and PD-L1 TPS by immunohistochemistry were prospectively collected. The association of smoking history with clinical outcomes of ICI monotherapy in metastatic NSCLC patients was evaluated after adjusting for other potential predictors.

Results

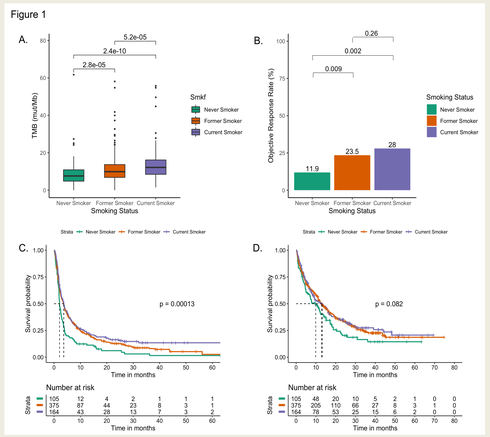
Table 1. Baseline clinicopathological characteristics

N=644				
Characteristics	**Never Smoker (n = 105)**	**Former Smoker (n = 375)**	**Current Smoker (n = 164)**	**P**
Age, median (range), years	63 (25-87)	69 (35-92)	63 (38-88)	<0.001
Gender, No. (%)				
Female	60 (57.1)	207 (55.2)	88 (53.0)	
Male	45 (42.9)	168 (44.8)	77 (47.0)	0.80
Histology, No. (%)				
Non-Squamous Cell Carcinoma	97 (92.4)	332 (88.5)	141 (86.0)	
Squamous Cell Carcinoma	8 (7.6)	43 (11.5)	23 (14.0)	0.27
ECOG PS, No. (%)				
0-1	82 (78.1)	298 (79.5)	123 (75.0)	
≥2	22 (21.0)	74 (19.7)	40 (24.4)	0.48
Unknown	1 (1.0)	3 (0.8)	1 (0.6)	
PD-L1 TPS, No. (%)				
Negative	20 (19.0)	48 (12.8)	12 (7.3)	
1-49%	23 (21.9)	86 (22.9)	41 (25.0)	
≥50%	30 (28.6)	137 (36.5)	56 (34.1)	0.07
Unknown	32 (30.5)	104 (27.7)	55 (33.5)	
Lines of therapy, No. (%)				
1L	18 (17.1)	139 (37.1)	59 (36.0)	
≥2L	87 (82.9)	236 (62.9)	105 (64.0)	<0.001
Pack-years, median (IQR)	0 (0)	28 (25)	40 (26.3)	<0.001
TMB, median (IQR), (mut/Mb)	7.6 (6.1)	9.9 (6.8)	12.2 (7.7)	<0.001

Results

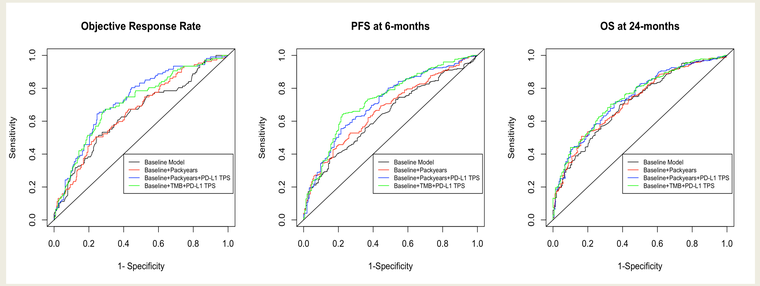
Predictive effect of smoking on clinical outcomes of ICI monotherapy

Figure 1



	Objective Response Rate		Progression-free Survival		Overall Survival	
Parameters	**OR (95% CI)**	**P**	**HR (95% CI)**	**P**	**HR (95% CI)**	**P**
Doubling Pack-years	1.21 (1.09, 1.36)	<0.001	0.92 (0.88, 0.95)	<0.001	0.94 (0.90, 0.99)	0.01
Age	1.01 (0.99, 1.03)	0.51	1.00 (0.99, 1.00)	0.23	1.00 (0.99, 1.01)	0.93
Male vs Female	0.74 (0.49, 1.10)	0.13	1.17 (0.99, 1.39)	0.06	1.22 (1.01, 1.47)	0.04
Squamous vs non-squamous	1.29 (0.70, 2.31)	0.41	1.05 (0.81, 1.36)	0.71	1.16 (0.88, 1.54)	0.30
ECOG PS ≥2 vs 0-1	0.30 (0.16, 0.53)	<0.001	2.03 (1.66, 2.48)	<0.001	2.99 (2.40, 3.73)	<0.001
ECOG PS Unknown vs 0-1	0.62 (0.03, 4.61)	0.68	0.77 (0.32, 1.86)	0.56	0.42 (0.10, 1.68)	0.22
PD-L1 TPS ≥50% vs Negative	4.14 (1.91, 10.06)	<0.001	0.54 (0.41, 0.72)	<0.001	0.63 (0.45, 0.87)	0.006
PD-L1 TPS 1-49% vs Negative	1.48 (0.64, 3.74)	0.38	0.88 (0.67, 1.17)	0.39	0.97 (0.71, 1.32)	0.85
Unknown vs Negative	2.25 (1.02, 5.50)	0.06	0.79 (0.61, 1.05)	0.11	0.96 (0.71, 1.28)	0.77
≥2L vs 1L treatment	0.90 (0.57, 1.43)	0.65	1.06 (0.86, 1.30)	0.61	1.30 (1.02, 1.65)	0.04

Clinical Utility - Predictive model performance on clinical outcomes of ICI monotherapy



Model (N = 451)	ORR	PFS	OS
Baseline Model	0.64 (0.53, 0.72)	0.62 (0.56, 0.67)	0.72 (0.65, 0.76)
Baseline+Pack-years	0.67 (0.54, 0.75)	0.65 (0.60, 0.70)	0.73 (0.66, 0.77)
Baseline+PD-L1 TPS+Pack-years	0.71 (0.61, 0.77)	0.66 (0.61, 0.71)	0.73 (0.67, 0.78)
Baseline+PD-L1 TPS+TMB	0.71 (0.63, 0.77)	0.68 (0.64, 0.72)	0.74 (0.68, 0.78)

*Baseline model incorporates age, gender, ECOG PS, Histology and Lines of Treatment

Conclusions & Relevance

- Increased smoking exposure had a significant association with improved clinical outcomes in metastatic NSCLC treated with ICI monotherapy independent of PD-L1 TPS.
- Smoking pack-years may serve as a consistent and readily obtainable surrogate of ICI efficacy when TMB is not available to inform prompt clinical decisions and enhance the proportion of patients who may benefit from ICIs.

Selected References

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