SUPPLEMENTARY MATERIALS

Supplementary Tables

Supplementary Table 1. Driver mutations by smoking status

Gene	Never Smoker, No. % (n=105)	Former Smoker, No. % (n=375)	Current Smoker, No. % (n=164)	Overall, No. % (N=644)
ALK	2 (1.9)	2 (0.5)	1 (0.6)	5 (0.8)
BRAF	3 (2.9)	10 (2.7)	9 (5.5)	22 (3.4)
EGFR	39 (37.1)	22 (5.9)	4 (2.4)	65 (10.1)
HER2	6 (5.7)	6 (1.6)	1 (0.6)	13 (2.0)
KRAS	12 (11.4)	154 (41.1)	64 (39.0)	230 (35.7)
MET	6 (5.7)	11 (2.9)	1 (0.6)	18 (2.8)
RET	3 (2.9)	4 (1.1)	0 (0)	7 (1.1)
ROS1	1 (1.0)	2 (0.5)	1 (0.6)	4 (0.6)
Wild-Type	33 (31.4)	164 (43.7)	83 (50.6)	280 (43.5)

Supplementary Table 2. Best overall response by smoking status

Best overall response	Never Smoker (n=105)		Former Smoker (n=375)		Current Smoker (n=164)	
	n	%	n	%	n	%
Complete response	2	1.9	4	1.1	2	1.2
Partial response	10	9.5	84	22.4	44	26.8
Stable disease	29	27.6	132	35.2	54	32.9
Progressive disease	64	61.0	155	41.3	64	39.0
Objective response rate (%)	11.4		23.5		28.0	

Supplementary Table 3. Association between smoking status and ORR, PFS and OS based on complete dataset and complete dataset using IPW[a]

Parameters	Objective Response Rate (n=451)				Progression-Free Survival (n=451)				Overall Survival (n=451)			
	Univariable analysis		Multivariable analysis		Univariable analysis		Multivariable analysis		Univariable analysis		Multivariable analysis	
	OR (95% CI)[b]	P[c]	OR (95% CI)[d]	P[c]	HR (95% CI)[e]	P[c]	HR (95% CI)[f]	P[c]	HR (95% CI)[e]	P[c]	HR (95% CI)[f]	P[c]
Complete dataset												
Former vs Never smoker	1.80 (0.92 3.78)	0.10	1.38 (0.67, 3.05)	0.40	0.65 (0.50, 0.86)	0.002	0.77 (0.58, 1.02)	0.07	0.77 (0.56, 1.05)	0.092	0.89 (0.64, 1.22)	0.48
Current vs Never smoker	2.24 (1.07, 4.99)	0.04	1.92 (0.87, 4.46)	0.12	0.60 (0.44, 0.83)	0.002	0.66 (0.48, 0.91)	0.01	0.73 (0.51, 1.06)	0.10	0.82 (0.57, 1.19)	0.29
Age	NA	NA	1.00 (0.98, 1.02)	0.99	NA	NA	1.00 (0.99, 1.01)	0.48	NA	NA	1.00 (1.00, 1.02)	0.13
Male vs Female	NA	NA	0.84 (0.52, 1.34)	0.47	NA	NA	1.10 (0.90, 1.35)	0.34	NA	NA	1.13 (0.89, 1.42)	0.32
Squamous vs Non-squamous	NA	NA	1.37 (0.64, 2.80)	0.39	NA	NA	1.09 (0.80, 1.49)	0.61	NA	NA	1.21 (0.84, 1.72)	0.30
ECOG PS ≥2 vs 0-1	NA	NA	0.36 (0.18, 0.70)	0.004	NA	NA	1.85 (1.46, 2.34)	<0.001	NA	NA	2.86 (2.19, 3.73)	<0.001
PD-L1 TPS	NA	NA	5.06 (2.60, 10.07)	<0.001	NA	NA	0.47 (0.35, 0.64)	<0.001	NA	NA	0.59 (0.41, 0.83)	0.003
≥2nd line vs 1st line treatment	NA	NA	0.73 (0.44, 1.21)	0.22	NA	NA	1.08 (0.86, 1.36)	0.49	NA	NA	1.46 (1.11, 1.91)	0.006
Complete Dataset using IPW												
Former vs Never smoker	1.10 (0.99, 1.22)	0.082	1.06 (0.95, 1.17)	0.31	0.65 (0.48, 0.87)	0.004	0.75 (0.55, 1.02)	0.062	0.78 (0.56, 1.09)	0.15	0.87 (0.60, 1.27)	0.48
Current vs Never smoker	1.13 (1.00, 1.27)	0.048	1.09 (0.97, 1.22)	0.15	0.61 (0.43, 0.86)	0.004	0.65 (0.46, 0.92)	0.020	0.73 (0.49, 1.08)	0.11	0.78 (0.52, 1.19)	0.26
Age	NA	NA	1.00 (1.00, 1.01)	0.89	NA	NA	0.99 (0.98, 1.01)	0.32	NA	NA	1.01 (0.99, 1.02)	0.35
Male vs Female	NA	NA	0.97 (0.90, 1.04)	0.41	NA	NA	1.11 (0.91, 1.37)	0.30	NA	NA	1.13 (0.88, 1.44)	0.35
Squamous vs Non-squamous	NA	NA	1.05 (0.93, 1.18)	0.42	NA	NA	1.08 (0.84, 1.39)	0.53	NA	NA	1.15 (0.81, 1.63)	0.45

ECOG PS ≥2 vs 0-1	NA	NA	0.89 (0.81, 0.98)	0.01	NA	NA	1.87 (1.42, 2.47)	<0.001	NA	NA	2.91 (2.10, 4.03)	<0.001
PD-L1 TPS	NA	NA	1.32 (1.19, 1.47)	<0.001	NA	NA	0.48 (0.35, 0.65)	<0.001	NA	NA	0.61 (0.43, 0.88)	0.007
≥2nd line vs 1st line treatment	NA	NA	0.95 (0.87, 1.04)	0.24	NA	NA	1.08 (0.86, 1.36)	0.49	NA	NA	1.47 (1.12, 1.93)	0.006

[a]Continuous PD-L1 TPS was included in the analysis. ECOG PS = Eastern Cooperative Oncology Group Performance Status; NA = not applicable;

PD-L1 TPS = programmed death ligand-1 tumor proportion score; TMB = tumor mutation burden. Inverse Probability Weighting (IPW).

[b]Unadjusted odds ratio (OR) of objective response.

[c] All P-values were two-sided.

[d]Odds ratio (OR) of objective response adjusted for age, gender, histology, ECOG PS, PD-L1 TPS and lines of treatment.

[e]Unadjusted hazard ratio (HR).

[f]Hazard ratio (HR) adjusted for age, gender, histology, ECOG PS, PD-L1 TPS and lines of treatment.

Supplementary Table 4. Association between smoking pack-years and ORR, PFS and OS based on complete dataset and complete dataset using IPW[a]

Parameters	Objective Response Rate (n=451)				Progression-Free Survival (n=451)				Overall Survival (n=451)			
	Univariable analysis		Multivariable analysis		Univariable analysis		Multivariable analysis		Univariable analysis		Multivariable analysis	
	OR (95% CI)[b]	P^c	OR (95% CI)[d]	P^c	HR (95% CI)[e]	P^c	HR (95% CI)[f]	P^c	HR (95% CI)[e]	P^c	HR (95% CI)[f]	P^c
Complete Dataset												
Doubling Pack-years	1.13 (1.01, 1.27)	0.042	1.12 (0.99, 1.28)	0.081	0.91 (0.87, 0.96)	<0.001	0.92 (0.88, 0.97)	0.001	0.95 (0.90, 1.00)	0.07	0.95 (0.90, 1.01)	0.082
Age	NA	NA	0.99 (0.97, 1.02)	0.65	NA	NA	1.00 (0.99, 1.01)	0.76	NA	NA	1.01 (1.00, 1.02)	0.07
Male vs Female	NA	NA	0.80 (0.49, 1.29)	0.36	NA	NA	1.15 (0.94, 1.41)	0.18	NA	NA	1.16 (0.91, 1.46)	0.23
Squamous vs Non-squamous	NA	NA	1.37 (0.65, 2.80)	0.39	NA	NA	1.09 (0.79, 1.50)	0.60	NA	NA	1.21 (0.85, 1.72)	0.30
ECOG PS ≥2 vs 0-1	NA	NA	0.37 (0.18, 0.70)	0.004	NA	NA	1.83 (1.44, 2.31)	<0.001	NA	NA	2.85 (2.19, 3.70)	<0.001
PD-L1 TPS	NA	NA	5.10 (2.63, 10.13)	<0.001	NA	NA	0.47 (0.35, 0.63)	<0.001	NA	NA	0.59 (0.41, 0.83)	0.003
≥2nd line vs 1st line treatment	NA	NA	0.73 (0.44, 1.21)	0.22	NA	NA	1.07 (0.85, 1.35)	0.55	NA	NA	1.45 (1.10, 1.89)	0.007
Complete Dataset using IPW												
Doubling Packyears	1.13 (1.01, 1.27)	0.04	1.12 (0.99, 1.28)	0.08	0.91 (0.87, 0.96)	<0.001	0.92 (0.88, 0.97)	0.001	0.95 (0.90, 1.00)	0.07	0.95 (0.90, 1.01)	0.08
Age	NA	NA	0.99 (0.97, 1.02)	0.65	NA	NA	1.00 (0.99, 1.01)	0.76	NA	NA	1.01 (1.00, 1.02)	0.07
Male vs Female	NA	NA	0.80 (0.49, 1.29)	0.36	NA	NA	1.15 (0.94, 1.41)	0.18	NA	NA	1.16 (0.91, 1.46)	0.23
Squamous vs Non-squamous	NA	NA	1.37 (0.65, 2.80)	0.39	NA	NA	1.09 (0.79, 1.50)	0.60	NA	NA	1.21 (0.85, 1.72)	0.30
ECOG performance status >=2 vs 0-1	NA	NA	0.37 (0.18, 0.70)	0.004	NA	NA	1.83 (1.44, 2.31)	<0.001	NA	NA	2.85 (2.19, 3.70)	<0.001
PD-L1 TPS	NA	NA	5.10 (2.63, 10.13)	<0.001	NA	NA	0.47 (0.35, 0.63)	<0.001	NA	NA	0.59 (0.41, 0.83)	0.003

| ≥2nd line vs 1st line treatment | NA | NA | 0.73 (0.44, 1.21) | 0.22 | NA | NA | 1.07 (0.85, 1.35) | 0.55 | NA | NA | 1.45 (1.10, 1.89) | 0.007 |

[a]Continuous PD-L1 TPS was included in the analysis. ECOG PS = Eastern Cooperative Oncology Group Performance Status; NA = not applicable;

PD-L1 TPS = programmed death ligand-1 tumor proportion score; TMB = tumor mutation burden. Inverse Probability Weighting (IPW).

[b]Unadjusted odds ratio (OR) of objective response.

[c] All P-values were two-sided.

[d]Odds ratio (OR) of objective response adjusted for age, gender, histology, ECOG PS, PD-L1 TPS and lines of treatment.

[e]Unadjusted hazard ratio (HR).

[f]Hazard ratio (HR) adjusted for age, gender, histology, ECOG PS, PD-L1 TPS and lines of treatment.

Supplementary Table 5. Association between packyears and ORR, PFS and OS in patients lacking oncogenic drivers and those with oncogenic driver mutations

Parameters	Objective Response Rate (n=510)				Progression-Free Survival (n=510)				Overall Survival (n=510)			
	Univariable analysis		Multivariable analysis		Univariable analysis		Multivariable analysis		Univariable analysis		Multivariable analysis	
	OR (95% CI)[a]	P[b]	OR (95% CI)[c]	P[b]	HR (95% CI)[d]	P[b]	HR (95% CI)[e]	P[b]	HR (95% CI)[d]	P[b]	HR (95% CI)[e]	P[b]
In patients lacking oncogenic drivers												
Packyears	1.14 (1.01, 1.30)	0.05	1.16 (1.01, 1.34)	0.04	0.96 (0.91, 1.01)	0.09	0.96 (0.90, 1.00)	0.06	0.98 (0.92, 1.04)	0.45	0.95 (0.89, 1.01)	0.11
Age	NA	NA	1.00 (0.98, 1.02)	0.94	NA	NA	1.00 (0.99, 1.01)	0.84	NA	NA	1.00 (0.99, 1.01)	0.56
Male vs Female	NA	NA	0.78 (0.50, 1.21)	0.27	NA	NA	1.21 (1.00, 1.46)	0.05	NA	NA	1.22 (0.99, 1.53)	0.06
Squamous vs Non-squamous	NA	NA	1.17 (0.62, 2.13)	0.61	NA	NA	1.09 (0.83, 1.43)	0.53	NA	NA	1.16 (0.87, 1.55)	0.32
ECOG PS ≥2 vs 0-1	NA	NA	0.32 (0.16, 0.59)	<0.001	NA	NA	1.96 (1.57, 2.45)	<0.001	NA	NA	2.99 (2.34, 3.82)	<0.001
ECOG PS Unknown vs 0-1	NA	NA	0.67 (0.03, 5.44)	0.73	NA	NA	0.81 (0.30, 2.19)	0.67	NA	NA	0.31 (0.04, 2.19)	0.24
PD-L1 TPS ≥50% vs Negative	NA	NA	3.41 (1.52, 8.50)	0.005	NA	NA	0.56 (0.41, 0.78)	<0.001	NA	NA	0.65 (0.45, 0.94)	0.02
PD-L1 TPS 1-49% vs Negative	NA	NA	1.44 (0.61, 3.73)	0.42	NA	NA	0.89 (0.65, 1.22)	0.47	NA	NA	1.07 (0.76, 1.52)	0.69
PD-L1 TPS Unknown vs Negative	NA	NA	2.15 (0.96, 5.32)	0.08	NA	NA	0.78 (0.58, 1.05)	0.11	NA	NA	0.98 (0.70, 1.36)	0.90
≥2nd line vs 1st line treatment	NA	NA	0.91 (0.55, 1.51)	0.71	NA	NA	1.02 (0.81, 1.28)	0.87	NA	NA	1.23 (0.94, 1.60)	0.13
In patients with oncogenic drivers												
Packyears	1.33 (1.08, 1.65)	0.008	1.35 (1.05, 1.79)	0.03	0.84 (0.78, 0.92)	<0.001	0.89 (0.81, 0.96)	0.005	0.91 (0.84, 1.00)	0.04	0.97 (0.89, 1.06)	0.52
Age	NA	NA	1.05 (0.99, 1.11)	0.11	NA	NA	0.97 (0.96, 0.99)	0.001	NA	NA	0.99 (0.97, 1.01)	0.37
Male vs Female	NA	NA	0.50 (0.15, 1.50)	0.23	NA	NA	0.89 (0.61, 1.31)	0.56	NA	NA	1.02 (0.67, 1.55)	0.93

Squamous vs Non-squamous	NA	NA	7.11 (0.18, 28.1)	0.25	NA	NA	1.33 (0.40, 4.46)	0.64	NA	NA	2.12 (0.48, 9.40)	0.32
ECOG PS ≥2 vs 0-1	NA	NA	0.20 (0.01, 1.33)	0.16	NA	NA	2.52 (1.52, 4.17)	<0.001	NA	NA	3.43 (2.01, 5.83)	<0.001
ECOG PS Unknown vs 0-1	NA	NA	NA	>0.99	NA	NA	0.49 (0.07, 3.62)	0.48	NA	NA	0.64 (0.09, 4.74)	0.66
PD-L1 TPS ≥50% vs Negative	NA	NA	NA	>0.99	NA	NA	0.29 (0.15, 0.57)	<0.001	NA	NA	0.48 (0.23, 1.00)	0.05
PD-L1 TPS 1-49% vs Negative	NA	NA	NA	>0.99	NA	NA	0.58 (0.30, 1.14)	0.11	NA	NA	0.56 (0.28, 1.12)	0.10
PD-L1 TPS Unknown vs Negative	NA	NA	NA	>0.99	NA	NA	0.66 (0.33, 1.29)	0.22	NA	NA	0.85 (0.42, 1.69)	0.64
≥2nd line vs 1st line treatment	NA	NA	0.99 (0.29, 3.60)	0.93	NA	NA	1.14 (0.66, 1.96)	0.63	NA	NA	1.70 (0.88, 3.26)	0.11

[a]Unadjusted odds ratio (OR) of objective response. ECOG PS = Eastern Cooperative Oncology Group Performance Status; NA = not applicable;

PD-L1 TPS = programmed death ligand-1 tumor proportion score; TMB = tumor mutation burden. Inverse Probability Weighting (IPW).

[b] All P-values were two-sided.

[c]Odds ratio (OR) of objective response adjusted for age, gender, histology, ECOG PS, PD-L1 TPS and lines of treatment.

[d]Unadjusted hazard ratio (HR).

[e]Hazard ratio (HR) adjusted for age, gender, histology, ECOG PS, PD-L1 TPS and lines of treatment.

Supplementary Table 6. Effect of smoking pack-years on ORR, OS, and PFS in stratified analysis by PD-L1 TPS of

≥50%[a]

Clinical outcomes	PD-L1 TPS <50% (n=230)			PD-L1 TPS ≥50% (n=221)		
	1st line	> 2nd line	Overall	1st line	> 2nd line	Overall
ORR						
Univariable						
OR (95% CI)	0.99 (0.68, 1.55)	1.11 (0.91, 1.40)	1.09 (0.91, 1.32)	1.10 (0.89, 1.38)	1.12 (0.90, 1.43)	1.14 (0.98, 1.33)
P[b]	0.95	0.34	0.39	0.39	0.32	0.10
Multivariable						
OR (95% CI)	1.09 (0.69, 1.86)	1.13 (0.91, 1.43)	1.13 (0.93, 1.39)	1.20 (0.95, 1.53)	1.18 (0.93, 1.53)	1.18 (1.01, 1.41)
P[b]	0.72	0.29	0.25	0.13	0.19	0.05
OS						
Univariable						
HR (95% CI)	0.98 (0.83, 1.17)	0.97 (0.90, 1.05)	0.97 (0.90, 1.04)	1.00 (0.85, 1.17)	0.91 (0.80, 1.03)	0.93 (0.85, 1.02)
P[b]	0.86	0.47	0.35	0.99	0.15	0.14
Multivariable						
HR (95% CI)	0.95 (0.79, 1.15)	1.00 (0.92, 1.08)	0.98 (0.92, 1.06)	0.90 (0.76, 1.05)	0.83 (0.72, 0.95)	0.87 (0.79, 0.96)
P[b]	0.61	0.98	0.64	0.19	0.007	0.007
PFS						
Univariable						
HR (95% CI)	0.93 (0.81, 1.07)	0.93 (0.87, 1.00)	0.93 (0.88, 0.99)	0.93 (0.82, 1.04)	0.89 (0.80, 1.00)	0.90 (0.84, 0.98)
P[b]	0.31	0.04	0.02	0.20	0.05	0.012
Multivariable						
HR (95% CI)	0.89 (0.77, 1.04)	0.95 (0.89, 1.02)	0.94 (0.89, 1.01)	0.89 (0.79, 1.00)	0.85 (0.76, 0.96)	0.88 (0.81, 0.95)
P[b]	0.15	0.21	0.09	0.06	0.008	0.002

[a]Multivariable analyses adjusted for age, gender, histology, ECOG PS, PD-L1 TPS and lines of treatment. ORR= objective response rate; PFS = progression-free survival; OS = overall survival; HR = hazard ratio; PD-L1 TPS = programmed death ligand-1 tumor proportional score; 1-line: first line of treatment, >2nd line: second lines of treatment and beyond

[b]All P-values were two-sided.

Supplementary Table 7. Effect of smoking pack-years on ORR, PFS and OS by different PD-L1 TPS cut-offs

PD-L1 TPS cutoff	ORR				PFS				OS			
	Below Cut-point		Above Cut-point		Below Cut-point		Above Cut-point		Below Cut-point		Above Cut-point	
	OR (95% CI)	P[a]	OR (95% CI)	P[a]	HR (95% CI)	P[a]	HR (95% CI)	P[a]	HR (95% CI)	P[a]	HR (95% CI)	P[a]
50%	1.13 (0.93, 1.40)	0.24	1.18 (1.01, 1.41)	0.047	0.95 (0.89, 1.01)	0.09	0.88 (0.81, 0.95)	0.002	0.98 (0.92, 1.06)	0.64	0.87 (0.79, 0.96)	0.007
55%	1.18 (0.98, 1.45)	0.09	1.18 (0.98, 1.45)	0.14	0.92 (0.87, 0.98)	0.01	0.89 (0.82, 0.98)	0.015	0.95 (0.89, 1.02)	0.18	0.89 (0.80, 0.99)	0.04
60%	1.18 (0.98, 1.45)	0.10	1.15 (0.97, 1.38)	0.12	0.92 (0.87, 0.98)	0.01	0.90 (0.82, 0.98)	0.01	0.95 (0.89, 1.02)	0.17	0.89 (0.80, 1.00)	0.04
70%	1.15 (0.98, 1.39)	0.11	1.14 (0.95, 1.39)	0.17	0.91 (0.86, 0.97)	0.004	0.90 (0.82, 0.99)	0.03	0.95 (0.89, 1.01)	0.12	0.89 (0.79, 1.00)	0.05

[a] All P-values were two-sided. ORR= objective response rate; PFS = progression-free survival; OS = overall survival; PD-L1 TPS = programmed death ligand-1 tumor proportional score; HR=hazard ratio.

Supplementary Table 8. Model performance based on complete dataset using IPW[a]

Model (n=451)	ORR AUC (95% CI)	PFS (6-months) AUC (95% CI)	OS (24-months) AUC (95% CI)
Baseline Model	0.64 (0.53, 0.72)	0.62 (0.56, 0.67)	0.72 (0.65, 0.77)
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 (0.62, 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)

[a]Predictive logistic and Cox proportional hazards models were constructed and validated in the complete dataset (n=451) with inverse probability weighting (IPW) using 10-fold cross-validation. Receiver operating characteristic's (ROC) area under the curve (AUC) illustrates the model performance on objective response rate (ORR), time-dependent AUC on progression-free survival (PFS) at 6 months and time-dependent AUC on overall survival (OS) at 24 months using different predictors. Baseline model incorporated age at treatment initiation, gender, histology, Eastern Cooperative Oncology Group Performance Status ECOG PS, and lines of treatment and they were consistently incorporated in all of the models. 95% CI was calculated from 500 bootstrapping.

Supplementary Table 9. Indirect effect of smoking status and smoking pack-years through TMB on ORR, PFS and OS[a]

Smoking variables	ORR				PFS				OS			
	Indirect Effect (OR)	Direct Effect (OR)	Total Effect (OR)	Prop	Indirect Effect (mo)	Direct Effect (mo)	Total Effect (mo)	Prop	Indirect Effect (mo)	Direct Effect (mo)	Total Effect (mo)	Prop
Smoking status												
Former vs Never Smoker	1.02 (<2e-16)	1.07 (0.10)	1.09 (0.04)	0.26 (0.04)	0.89 (0.004)	1.90 (0.12)	2.79 (0.02)	0.32 (0.03)	1.93 (0.002)	2.87 (0.50)	4.80 (0.23)	0.40 (0.23)
Current vs Never Smoker	1.05 (<2e-16)	1.10 (0.06)	1.16 (0.02)	0.34 (0.02)	2.04 (<2e-16)	2.92 (0.11)	4.96 (0.002)	0.41 (0.002)	4.00 (<2e-16)	2.71 (0.57)	6.71 (0.16)	0.60 (0.16)
Smoking Pack-year												
10 PY vs Never Smoker	1.03 (<0.001)	1.05 (<0.001)	1.08 (<0.001)	0.33 (<0.001)	0.94 (<0.001)	1.76 (0.016)	2.70 (<0.001)	0.35 (<0.001)	1.97 (<0.001)	3.63 (0.068)	5.59 (0.004)	0.35 (0.004)
20 PY vs Never Smoker	1.04 (<0.001)	1.07 (0.04)	1.11 (0.04)	0.33 (<0.001)	1.24 (<0.001)	2.32 (0.008)	3.55 (<0.001)	0.35 (<0.001)	2.57 (<0.001)	4.73 (0.108)	7.29 (0.004)	0.35 (0.004)
30 PY vs Never Smoker	1.04 (<0.001)	1.08 (0.08)	1.13 (<0.001)	0.33 (<0.001)	1.47 (<0.001)	2.74 (0.016)	4.20 (<0.001)	0.35 (<0.001)	3.01 (<0.001)	5.55 (0.104)	8.56 (0.012)	0.35 (0.012)
20 PY vs 10 PY	1.01 (<0.001)	1.02 (<0.001)	1.03 (<0.001)	0.33 (<0.001)	0.32 (<0.001)	0.60 (0.004)	0.93 (<0.001)	0.35 (<0.001)	0.62 (<0.001)	1.15 (0.112)	1.77 (0.004)	0.35 (0.004)
30 PY vs 20 PY	1.00 (<0.001)	1.01 (<0.001)	1.02 (<0.001)	0.33 (<0.001)	0.21 (<0.001)	0.40 (0.012)	0.72 (<0.001)	0.35 (<0.001)	0.40 (<0.001)	0.74 (0.148)	1.14 (0.008)	0.35 (0.008)

[a]Mediated effect through TMB by smoking status. Mediated effect on ORR is in the unit of Odds Ratio (OR) while progression-free survival (PFS) and overall survival (OS) is in the unit of months. Prop: proportion of the mediated effect through smoking variables; PY; smoking pack-years.

Supplementary Table 10. Association between smoking status and TMB[a]

Covariates	Univariable Analysis (N=644)		Multivariable Analysis (N=644)	
	Effect (95% CI)	P[b]	Effect (95% CI)	P[b]
Former vs never smoker	1.36 (1.15, 1.61)	<0.001	1.35 (1.13, 1.60)	<0.001
Current vs never smoker	1.80 (1.49, 2.18)	<0.001	1.80 (1.49, 2.18)	<0.001
Age	NA	NA	1.00 (1.00, 1.01)	0.59
Male vs Female	NA	NA	1.08 (0.96,1.22)	0.21
Squamous Cell Carcinoma vs Non-Squamous Cell Carcinoma	NA	NA	0.95 (0.78, 1.14)	0.56

[a]Effect here means the difference of tumor mutation burden (TMB) comparing former smokers to never

smokers and current smokers to never smokers.

[b]All P-values were two-sided.

Supplementary Table 11. Model Performance using time-dependent AUC based on the complete dataset

Model (n=451)	ORR AUC (95% CI)	PFS (6-months) AUC (95% CI)	OS (24-months) AUC (95% CI)
Complete dataset[a]			
Baseline Model	0.64 (0.53, 0.72)	0.62 (0.56, 0.67)	0.72 (0.65, 0.76)
Baseline + PD-L1 TPS	0.69 (0.59, 0.75)	0.64 (0.59, 0.68)	0.73 (0.67, 0.77)
Baseline + Pack-years	0.67 (0.54, 0.75)	0.65 (0.60, 0.70)	0.73 (0.66, 0.77)
Baseline + TMB	0.66 (0.55, 0.73)	0.67 (0.62, 0.72)	0.73 (0.67, 0.78)
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 + PD-L1 TPS + TMB+ Pack-years	0.71 (0.63, 0.78)	0.69 (0.64, 0.73)	0.74 (0.68, 0.79)
Complete dataset with IPW[b]			
Baseline Model	0.64 (0.53, 0.72)	0.62 (0.56, 0.67)	0.72 (0.65, 0.77)
Baseline + PD-L1 TPS	0.69 (0.59, 0.75)	0.64 (0.59, 0.68)	0.73 (0.67, 0.77)
Baseline + Pack-years	0.67 (0.54, 0.75)	0.65 (0.60, 0.70)	0.73 (0.66, 0.77)
Baseline + TMB	0.66 (0.55, 0.73)	0.68 (0.62, 0.72)	0.73 (0.67, 0.78)
Baseline + PD-L1 TPS + Pack-years	0.71 (0.62, 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 + PD-L1 TPS + TMB + Pack-years	0.71 (0.63, 0.78)	0.69 (0.64, 0.73)	0.74 (0.68, 0.79)

[a]Predictive logistic and Cox proportional hazards models were constructed and validated the patients with complete information (n=451) using 10-fold cross-validation. Receiver operating characteristic's (ROC) area under the curve (AUC) illustrates the model performance on objective response rate (ORR), time-dependent AUC on progression-free survival (PFS) at 6 months and time-dependent AUC on overall survival (OS) at 24 months using different predictors. Baseline model incorporated age at treatment initiation, gender, histology, Eastern Cooperative Oncology Group Performance Status (ECOG PS), and lines of treatment and they were consistently incorporated in all of the models. 95% CI was calculated from 500 bootstrapping.

[b]Predictive logistic and Cox proportional hazards models were constructed and validated in the complete dataset (n=451) with inverse probability weighting (IPW) using 10-fold cross-validation. Receiver operating characteristic's (ROC) area under curve (AUC) illustrating the model performance on objective response rate (ORR), time-dependent AUC on progression-free survival (PFS) at 6 months and time-dependent AUC on overall survival (OS) at 24 months using different predictors. Baseline model incorporated age at treatment initiation, gender, histology, Eastern Cooperative Oncology Group Performance Status (ECOG PS), and lines of treatment and they were consistently incorporated in all of the models. 95% CI was calculated from 500 bootstrapping.

Supplementary Table 12. Model Performance using C-index based on the complete dataset and the complete dataset with IPW

Model (n=451)	ORR C-index (95% CI)	PFS C-index (95% CI)	OS C-index (95% CI)
Complete dataset[a]			
Baseline Model	0.64 (0.53, 0.72)	0.61 (0.53, 0.67)	0.55 (0.37, 0.74)
Baseline + PD-L1 TPS	0.69 (0.59, 0.75)	0.62 (0.54, 0.67)	0.63 (0.45, 0.76)
Baseline + Pack-years	0.67 (0.54, 0.75)	0.62 (0.54, 0.68)	0.58 (0.40, 0.73)
Baseline + TMB	0.66 (0.55, 0.73)	0.63 (0.56, 0.70)	0.56 (0.39, 0.72)
Baseline + PD-L1 TPS + Pack-years	0.71 (0.61, 0.77)	0.63 (0.56, 0.68)	0.64 (0.43, 0.78)
Baseline + PD-L1 TPS + TMB	0.71 (0.63, 0.77)	0.64 (0.58, 0.70)	0.64 (0.43, 0.78)
Baseline + PD-L1 TPS +TMB+ Pack-years	0.71 (0.63, 0.78)	0.65 (0.58, 0.70)	0.64 (0.45, 0.79)
Complete dataset with IPW[b]			
Baseline Model	0.64 (0.53, 0.72)	0.61 (0.53, 0.67)	0.55 (0.37, 0.74)
Baseline + PD-L1 TPS	0.69 (0.59, 0.75)	0.62 (0.54, 0.67)	0.63 (0.45, 0.76)
Baseline + Pack-years	0.67 (0.54, 0.75)	0.62 (0.54, 0.68)	0.58 (0.40, 0.73)
Baseline + TMB	0.66 (0.55, 0.73)	0.63 (0.56, 0.69)	0.56 (0.39, 0.72)
Baseline + PD-L1 TPS + Pack-years	0.71 (0.62, 0.77)	0.63 (0.56, 0.68)	0.64 (0.43, 0.78)
Baseline + PD-L1 TPS + TMB	0.71 (0.63, 0.77)	0.64 (0.57, 0.70)	0.64 (0.43, 0.78)
Baseline + PD-L1 TPS + TMB + Pack-years	0.71 (0.63, 0.78)	0.65 (0.58, 0.70)	0.64 (0.45, 0.79)

[a]Predictive logistic and Cox proportional hazards models were constructed and validated in the complete dataset (n=451) using 10-fold cross-validation. C-index illustrates the model performance on objective response rate (ORR), progression-free survival (PFS) and overall survival (OS) using different predictors. Baseline model incorporated age at treatment initiation, gender, histology, Eastern Cooperative Oncology Group Performance Status (ECOG PS), and lines of treatment and they were consistently incorporated in all of the models. 95% CI was calculated from 500 bootstrapping.

[b]Predictive logistic and Cox proportional hazards models were constructed and validated in the complete dataset (n=451) with inverse probability weighting (IPW) using 10-fold cross-validation. C-index illustrates the model performance on objective response rate (ORR), progression-free survival (PFS) and overall survival (OS) using different predictors. Baseline model incorporated age at treatment initiation, gender, histology, Eastern Cooperative Oncology Group Performance Status (ECOG PS), and lines of treatment and they were consistently incorporated in all of the models. 95% CI was calculated from 500 bootstrapping.

Supplementary Table 13. Baseline clinicopathological characteristics

Characteristics	PD-L1 TPS missing status			Lines of ICI Monotherapy			Oncogenic driver mutation status		
	PD-L1 unknown (n=191)	PD-L1 known (n=453)	P^a	1st line (n=216)	≥2nd line (n=428)	P^a	With oncogenic (n=134)	Without oncogenic (n=510)	P^a
Median age [range], y	64 [32.0, 91.0]	67 [25.0, 92.0]	0.001	69.0 [45.0, 92.0]	65.0 [25.0, 91.0]	<0.001	64.0 [25.0, 92.0]	66.5 [32.0, 91.0]	0.07
Gender, No. (%)			0.022						
Female	91 (47.6)	263 (58.1)		117 (54.2)	237 (55.4)	0.84	75 (56.0)	279 (54.7)	0.87
Male	100 (52.4)	190 (41.9)		99 (45.8)	191 (44.6)		59 (44.0)	231 (45.3)	
Histology, No. (%)			0.22						
Non-squamous Cell Carcinoma	164 (85.9)	406 (89.6)		188 (87.0)	382 (89.3)	0.48	131 (97.8)	439 (86.1)	<0.001
Squamous Cell Carcinoma	27 (14.1)	47 (10.4)		28 (13.0)	46 (10.7)		3 (2.2)	71 (13.9)	
Smoking status, No. (%)									
Never Smoker	32 (16.8)	73 (16.1)	0.39	18 (8.3)	87 (20.3)	<0.001	60 (44.8)	45 (8.8)	<0.001
Former Smoker	104 (54.5)	271 (59.8)		139 (64.4)	236 (55.1)		57 (42.5)	318 (62.4)	
Current Smoker	55 (28.8)	109 (24.1)		59 (27.3)	105 (24.5)		17 (12.7)	147 (28.8)	
ECOG PS, No. (%)									
0-1	151 (79.1)	351 (77.7)	0.59	173 (80.1)	330 (77.1)	0.61	108 (80.6)	395 (77.5)	0.50
≥2	37 (19.4)	99 (21.9)		43 (19.9)	93 (21.7)		25 (18.7)	111 (21.8)	
Unknown	3 (1.6)	2 (0.4)		0 (0)	5 (1.2)		1 (0.7)	4 (0.8)	
Lines of therapy, No. (%)									
1st line	20 (10.5)	196 (43.3)	<0.001	--	--	--	32 (23.9)	184 (36.1)	0.01
≥2nd line	171 (89.5)	257 (56.7)		--	--		102 (76.1)	326 (63.9)	
Pack-years, median (IQR) or [range]	29.5 (37.0)	25 (31.0)	0.85	25.0 [0, 120]	25.0 [0, 120]	0.02	3.00 [0, 120]	30.0 [0, 120]	<0.001
Unknown	--	--		0 (0)	1 (0.2)		1 (0.7)	0 (0)	
Median TMB (mut/Mb) (IQR) or [range]	9.68 (7.5)	9.89 (6.8)	0.86	10.6 [0, 41.8]	9.78 [0, 61.7]	0.11	9.12 [0, 41.8]	10.6 [0, 61.7]	0.005
PD-L1 TPS, No. (%)									
Negative	--	--	--	14 (6.5)	66 (15.4)	<0.001	13 (9.7)	67 (13.1)	0.39
1-49%	--	--		37 (17.1)	113 (26.4)		36 (26.9)	114 (22.4)	
≥50%	--	--		145 (67.1)	78 (18.2)		47 (35.1)	176 (34.5)	
Unknown	--	--		20 (9.3)	171 (40.0)		38 (28.4)	153 (30.0)	

[a]All P-values were two-sided. ECOG PS = Eastern Cooperative Oncology Group Performance Status; PD-L1 TPS = programmed death ligand-1
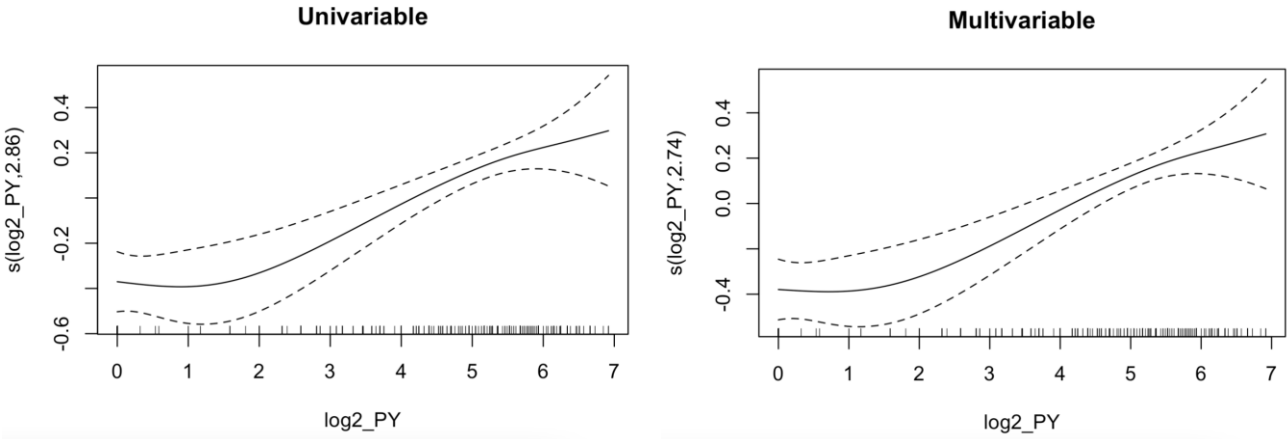
tumor proportion score; TMB = tumor mutation burden.

Supplementary Table 14. Univariate analysis of related clinical variables

Parameters	Objective Response Rate		Progression-free Survival		Overall Survival	
	OR (95% CI)	P^a	HR (95% CI)	P^a	HR (95% CI)	P^a
Former vs Never smoker	1.13 (1.03, 1.23)	0.009	0.66 (0.53, 0.83)	<0.001	0.77 (0.60, 0.99)	0.04
Current vs Never smoker	1.18 (1.07, 1.31)	0.001	0.59 (0.45, 0.76)	<0.001	0.74 (0.56, 0.99)	0.04
Doubling Pack-years	1.03 (1.01, 1.04)	<0.001	0.91 (0.88, 0.95)	<0.001	0.95 (0.91, 0.99)	0.02
Age	1.00 (0.99, 1.00)	0.23	1.00 (0.99, 1.01)	0.42	1.00 (0.99, 1.01)	0.54
Male vs Female	0.96 (0.90, 1.03)	0.28	1.13 (0.96, 1.33)	0.15	1.19 (0.99, 1.44)	0.058
Squamous vs Non-squamous	1.03 (0.93, 1.15)	0.51	1.08 (0.84, 1.39)	0.57	1.17 (0.89, 1.54)	0.27
ECOG PS ≥2 vs 0-1	0.85 (0.79, 0.92)	<0.001	1.96 (1.61, 2.38)	<0.001	2.88 (2.32, 3.57)	<0.001
ECOG PS unknown vs 0-1	0.94 (0.65, 1.36)	0.75	0.73 (0.30, 1.76)	0.48	0.42 (0.10, 1.68)	0.22
PD-L1 TPS ≥50% vs Negative	1.27 (1.15, 1.41)	<0.001	0.49 (0.37, 0.64)	<0.001	0.53 (0.39, 0.72)	<0.001
PD-L1 TPS 1-49% vs Negative	1.05 (0.94, 1.18)	0.35	0.85 (0.65, 1.12)	0.26	0.96 (0.71, 1.31)	0.81
Unknown vs Negative	1.11 (1.00, 1.24)	0.06	0.74 (0.57, 0.97)	0.03	0.92 (0.70, 1.23)	0.59
≥2nd line vs 1st line treatment	0.89 (0.84, 0.96)	<0.001	1.34 (1.12, 1.60)	0.002	1.56 (1.27, 1.93)	<0.001

[a] All P-values were two-sided. ECOG PS = Eastern Cooperative Oncology Group Performance Status; PD-
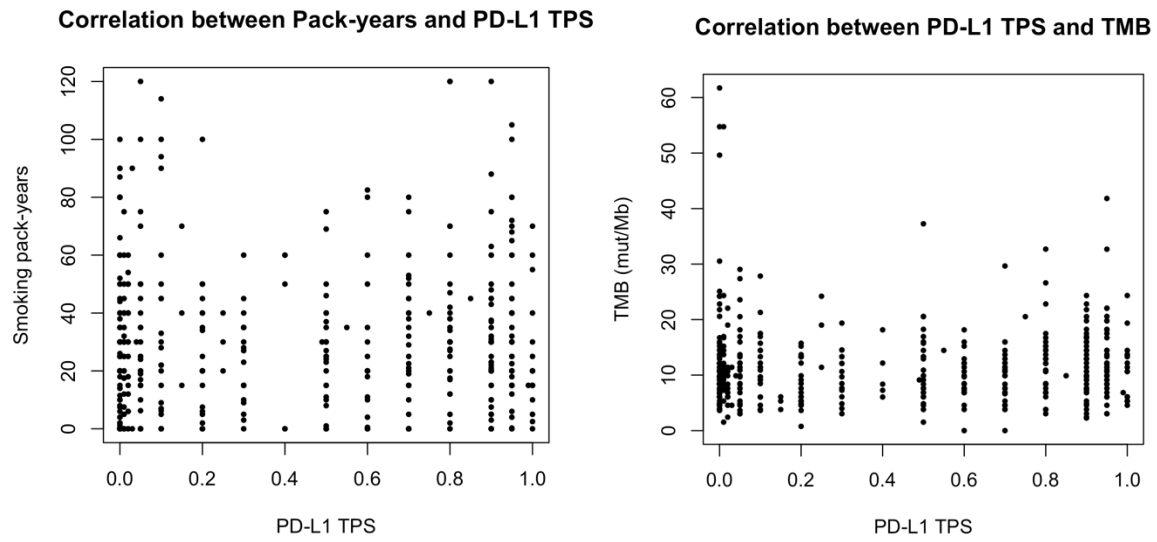
L1 TPS = programmed death ligand-1 tumor proportion score; TMB = tumor mutation burden.

Supplementary Figures

Supplementary Figure 1. Contribution of smoking pack-years to TMB
TMB = tumor mutation burden, PY = smoking pack-years

Supplementary Figure 2. Correlation between PD-L1 TPS and smoking pack-years and TMB.

PD-L1 TPS = Programmed death ligand-1 tumor proportion score; TMB = tumor mutation burden

Supplementary Figure 3. Correlation matrix between independent variables

Gender: Female, Male; Eastern Cooperative Oncology Group Performance Status (ECOG PS): 0-1, ≥2, Unknown; Path_bin: Non-SQ (Non-squamous Cell Carcinoma), SQ (Squamous Cell Carcinoma); Smkf: Never smoker, Former smoker and Current smoker; Trt_bin: First-Line, Second-line treatment setting and beyond. Color represents the smoking status with red: never smokers, green: former smokers and blue: current smokers.