

**XXI CONGRESSO
NAZIONALE SITAB
SOCIETÀ ITALIANA DI
TABACCOLOGIA**

PISA

**27-28
NOVEMBRE
2025**



Target therapy nel NSCLC: Differenze tra fumatori e non fumatori

Andrea Sbrana

SD Oncopneumologia

Dipartimento Oncologico

AOU Pisana

The mystery rise of lung cancer in non-smokers

6 June 2025

Share  Save 

Theres Lüthi



NSCLC: two worlds apart

Smoking-
related
NSCLC

Non smoking-
related
NSCLC

Different oncogenic pathways

Yano T et al, Int J Clin Oncol 2011

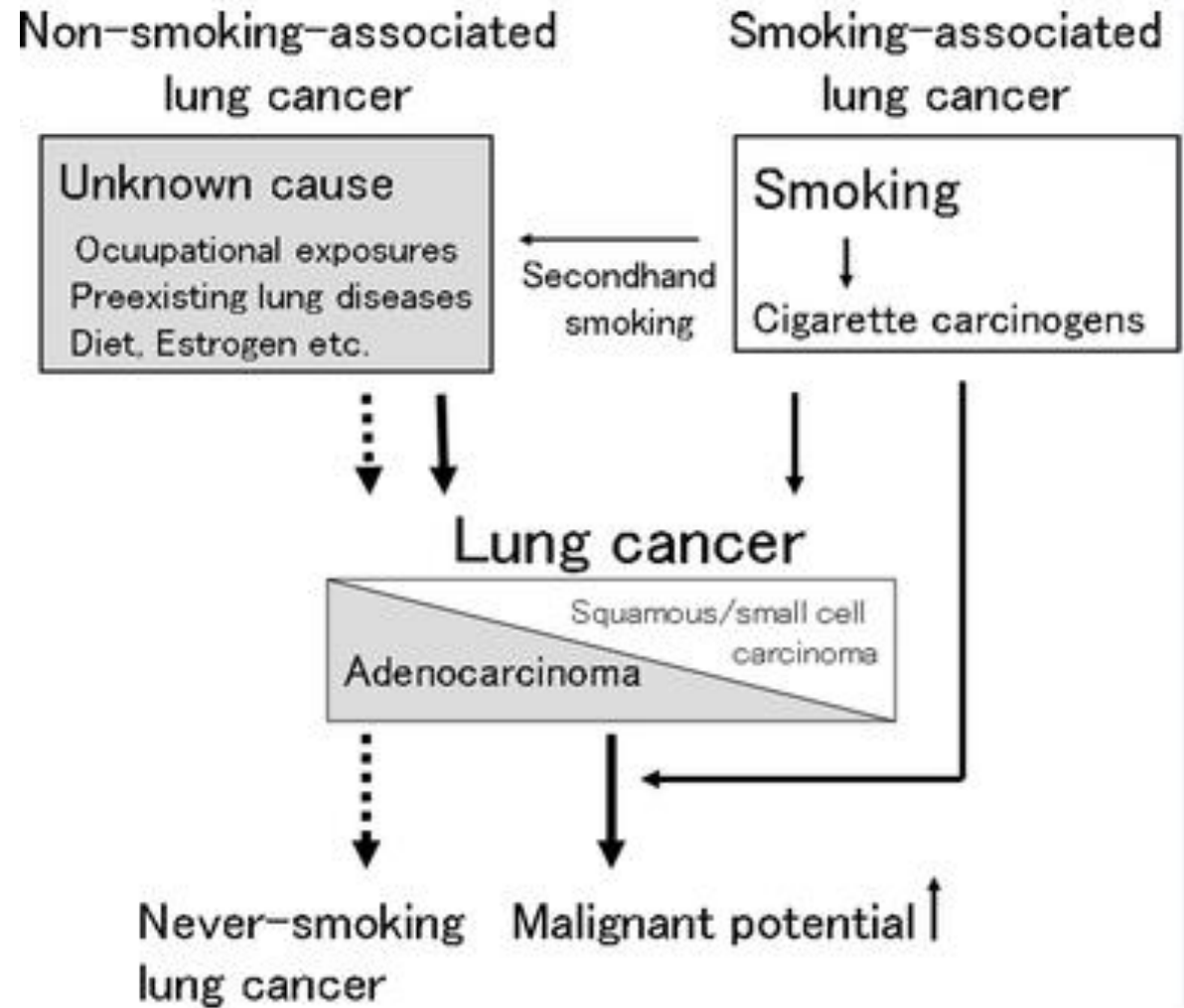


Table 1 Baseline patient characteristics

Variable	Ever-smoker [n = 88]	Never-smoker [n = 67]	p value
Smoking status, n (%)			–
Current smoker	15 (17)		
Prior smoker	73 (83)		
Never smoker	0 (0)	67 (100)	
Pack years of smoking, median (IQR) ^a	35 (20, 60)	0 (0, 0)	–
Female sex, n (%)	37 (42)	45 (67)	0.002
Age, mean ± SD ^a , years	69 ± 8	62 ± 13	<0.001
min–max	52–90	22–87	
Race/ethnicity, n (%)			0.67
African American	1 (1)	2 (3)	
Latinx	5 (6)	6 (9)	
White	76 (86)	56 (84)	
Other	6 (7)	3 (4)	
Body mass index, mean ± SD, kg/m ²	26 ± 6	26 ± 6	0.73
Family history of lung cancer, n (%)	11 (12)	8 (12)	0.94
History of chronic obstructive pulmonary disease (COPD), n (%)	42 (48)	1 (1)	<0.001
History of interstitial lung disease (ILD), n (%)	0 (0)	1 (1)	0.43
Type of ILD, n (%)			
Usual interstitial pneumonia (UIP), n (%)	0 (0)	1 (1)	0.43
History of non-lung cancer, n (%)	25 (37)	33 (38)	0.98
History of prior radiation therapy to the chest or neck, n (%)	3 (3)	3 (4)	>0.99
Known history of asbestos exposure, n (%)	3 (3)	1 (1)	0.63
History of type 2 diabetes mellitus (DM), n (%)	19 (22)	12 (18)	0.57
History of chronic liver disease, n (%)	3 (3)	3 (4)	>0.99
History of chronic kidney disease, n (%)	6 (7)	1 (1)	0.14

^a IQR interquartile range (25th, 75th percentile), SD standard deviation; boldface values indicate statistical significance

Different
clinical
characteristic
s

Table 5 Comparison of AJCC TNM stages by smoking status

TNM stage	Ever-smoker		Never-smoker	
	N (%)	N (%)	N (%)	p value
All patients	88	67		
T-stage				0.054
T1a	4 (4.5)	1 (1.5)		
T1b	13 (14.8)	11 (16.4)		
T1c	7 (8.0)	2 (3.0)		
T2	2 (2.3)	8 (11.9)		
T2a	14 (15.9)	12 (17.9)		
T2b	10 (11.4)	5 (7.5)		
T3	14 (15.9)	9 (13.4)		
T4	24 (27.3)	19 (28.4)		
N-stage				0.002
N0	46 (52.3)	25 (37.3)		
N1	10 (11.4)	15 (22.4)		
N2	16 (18.2)	20 (29.9)		
N3	16 (18.2)	7 (10.4)		
M-stage				0.004
M0	57 (64.8)	33 (49.3)		
M1	3 (3.4)	0 (0)		
M1a	10 (11.4)	9 (13.4)		
M1b	5 (5.7)	9 (13.4)		
M1c	11 (12.5)	16 (23.9)		
M2	2 (2.3)	0 (0)		
AJCC 8th Edition stage				0.046
IA	1 (1.1)	0 (0)		
IA1	2 (2.3)	0 (0)		
IA2	12 (13.6)	8 (11.9)		
IA3	3 (3.4)	0 (0)		
IB	10 (11.4)	3 (4.5)		
IIA	5 (5.7)	2 (3.0)		
IIB	4 (4.5)	7 (10.4)		
IIIA	10 (11.4)	5 (7.5)		
IIIB	7 (8.0)	3 (4.5)		
IIIC	4 (4.5)	1 (1.5)		
IVA	14 (15.9)	19 (28.4)		
IVB	16 (18.2)	19 (28.4)		

Boldface values indicate statistical significance

NSs tend to
be diagnosed
in M1-stage

Pathology			
Fine needle aspiration (FNA), n (%)	82 (93)	53 (80)	0.02
Cell type, n (%)			< 0.001
Adenocarcinoma	42 (48)	51 (76)	
Adenosquamous	2 (2)	1 (1)	
Squamous	38 (43)	10 (15)	
Large cell	0 (0)	1 (1)	
Poorly differentiated	6 (7)	4 (6)	
Surgical excision, n (%)	25 (28)	32 (48)	0.01
Cell type on surgical path, n/N (%)			0.22
Adenocarcinoma	14/25 (56)	23/32 (72)	
Adenosquamous	1/25 (4)	0/32 (0)	
Squamous	10/25 (40)	8/32 (25)	
Large cell	0/25 (0)	0/32 (0)	
Poorly differentiated	0/25 (0)	1/32 (3)	
Subtype (if applicable), n/N (%)			0.21
Acinar	8/15 (53)	6/24 (25)	
Papillary	0/15 (0)	4/24 (17)	
Bronchoalveolar	0/15 (0)	3/24 (12)	
Poorly differentiated	4/15 (27)	7/24 (7)	
Other	0/15 (0)	1/24 (1)	
Acinar and papillary	2/15 (13)	2/24 (8)	
Acinar and papillary and bronchoalveolar	0/15 (0)	1/24 (4)	
Acinar and large cell	1/15 (0)	0/24 (0)	
Size of tumor, mean ± SD, cm ³	30 ± 83	30 ± 59	0.98
Greatest dimension, mean ± SD, mm	28 ± 15	29 ± 21	0.87
Tumor genotype, n (%)			< 0.001
No genotyping	32 (37)	18 (29)	
EGFR	6 (7)	20 (32)	
ALK	1 (1)	6 (10)	
MET	1 (1)	0 (0)	
BRAF	1 (1)	3 (5)	
RAS	8 (9)	1 (2)	
HER2	1 (1)	2 (3)	
Other	33 (38)	9 (15)	
EGFR and other	0 (0)	1 (2)	
EGFR and ALK	0 (0)	2 (3)	
EGFR and RAS	1 (1)	0 (0)	
HER2 and other	1 (1)	0 (0)	
ROS1 and other	1 (1)	0 (0)	
Lymphovascular invasion, n (%)	9/25 (36)	9/27 (33)	0.84
Pleural invasion, n (%)	12/25 (48)	9/27 (33)	0.28

Different
pathology
characteristic
s

Burt et al, BMC Medicine 2025

Smoking history impacts on prognosis, but its impact on targeted treatment response is more debated

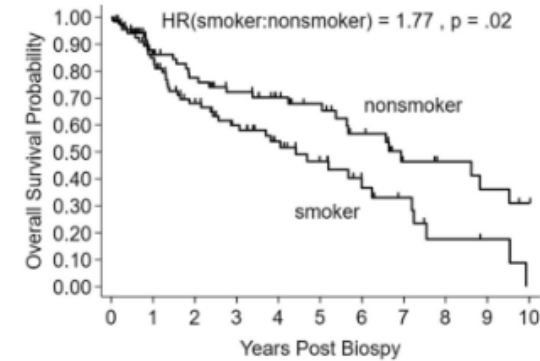


Fig. 2 Overall survival (absence of all-cause mortality) Kaplan-Meier graph. The 10-year hazard ratio (HR) and p value are from a Cox regression with all-cause mortality as the outcome variable. Tick marks on the survival curves represent censoring events (time points where at least one patient was lost to follow-up)

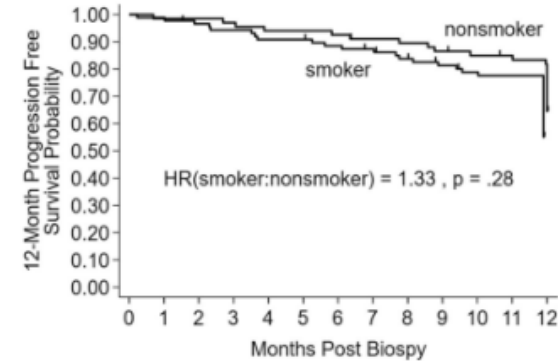
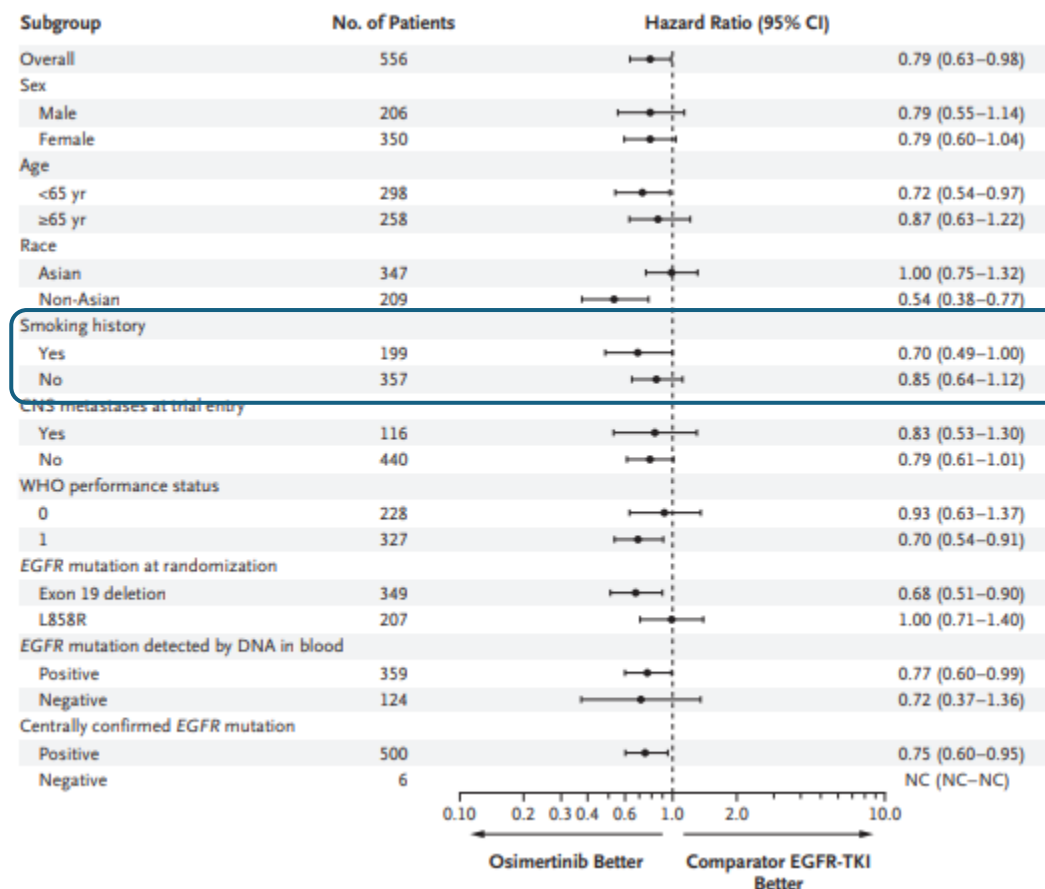


Fig. 3 12-month progression-free survival (absence of disease progression or death at the 12-month time point) Kaplan-Meier graph. The 1-year hazard ratio (HR) and p value are from a Cox regression with the composite score (disease progression or death) as the outcome variable. Tick marks on the survival curves represent censoring events (time points where at least one patient was lost to follow-up). A loss-to-follow-up occurred if the patient's last visit was before 12 months. The drop in the graph at 12 months is due to patients still in a state of disease progression at the 12-month time point (a small amount of jitter was added so the lines are distinguishable at the 12-month time point)

EGFr-mutant NSCLC

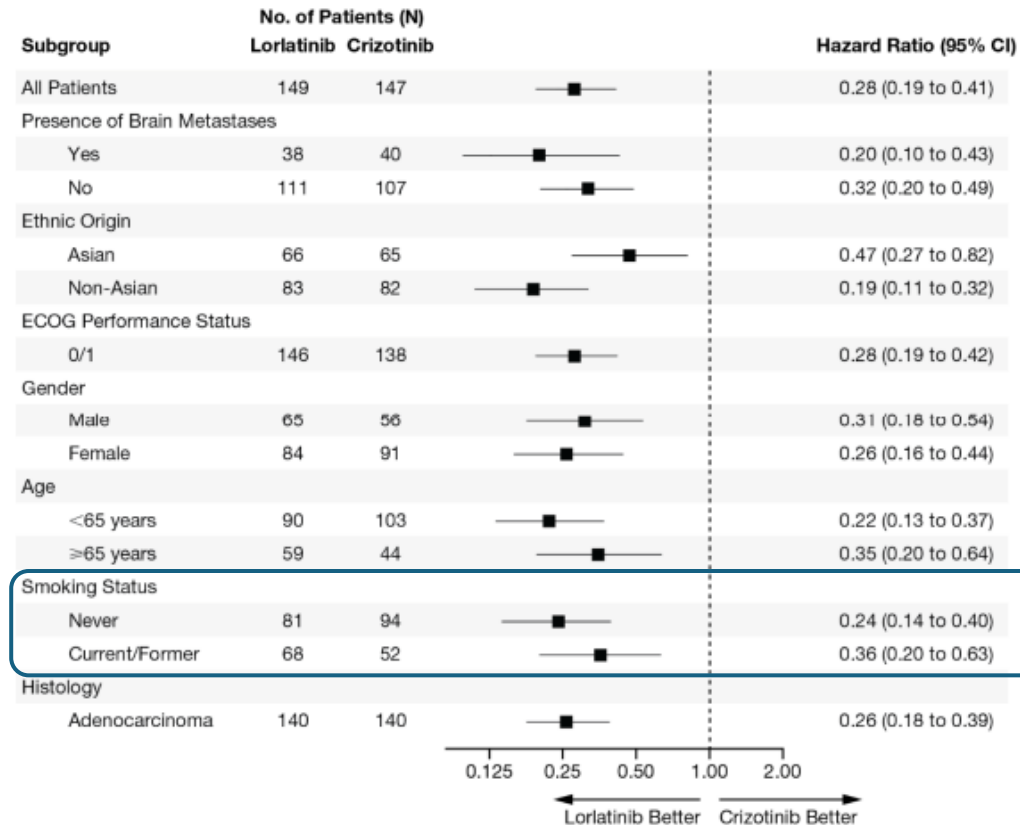
- Osimertinib is the standard first-line tx for EGFr-mutant mNSCLC.



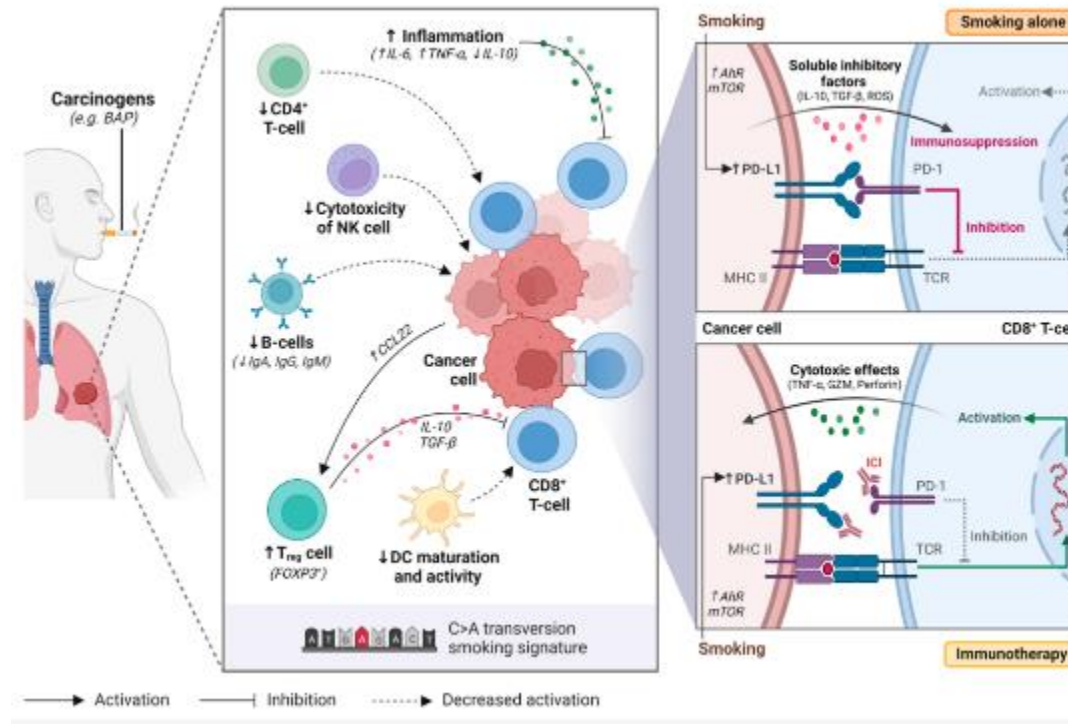
ALK-rearranged NSCLC

- Lorlatinib is the standard first-line tx for ALK-rearranged m

Figure S1. Forest plot of BICR-assessed PFS by patient subgroups



NSCLC in immunotherapy: smoking status is a key information



NSCLC in immunotherapy: smoking status is a key information

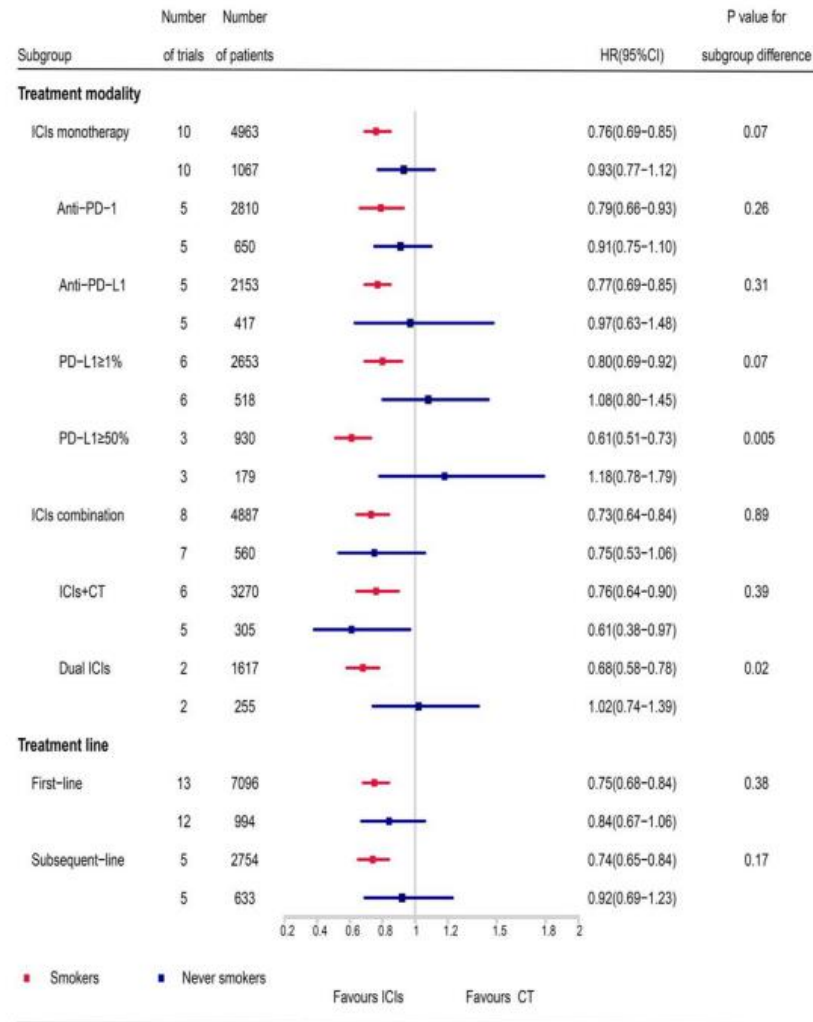


Fig. 4. Subgroup analyses for overall survival. HR, hazard ratio; CI, confidence interval; ICIs, immune checkpoint inhibitors; CT, chemotherapy.

NSCLC in immunotherapy: smoking status is a key information

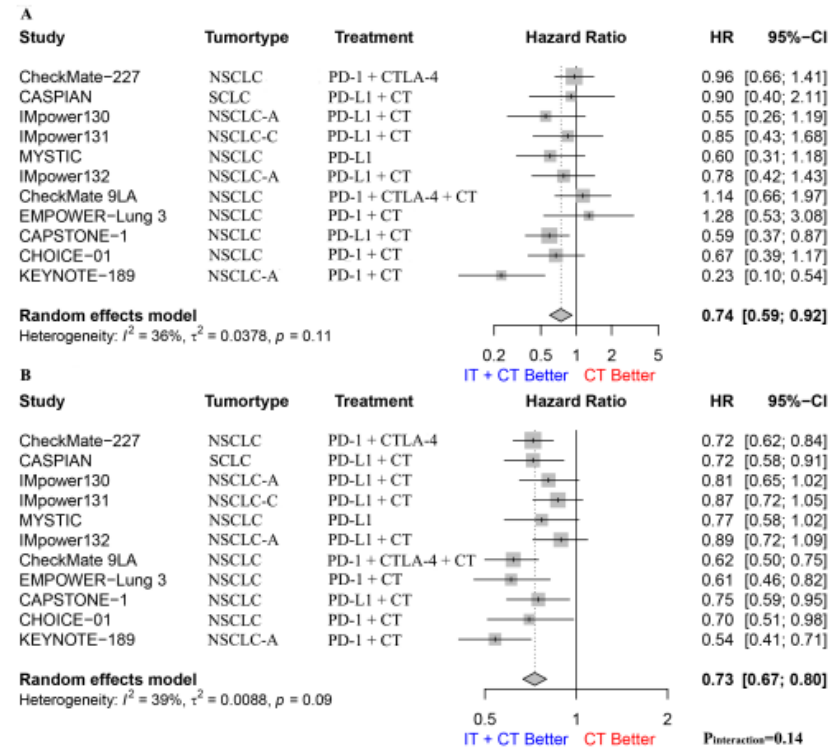


FIGURE 3
(A) The Hazard ratio for OS between immunotherapy combined with chemotherapy and chemotherapy alone in nonsmoking patients; **(B)** The Hazard ratio for OS between immunotherapy combined with chemotherapy and chemotherapy alone in smoking patients. The P interaction was calculated from the meta-analyzed HRs of nonsmokers and smokers. NSCLC, non-small-cell lung cancer; NSCLC-A, non-squamous non-small-cell lung cancer; NSCLC-C, squamous non-small-cell lung cancer; CT, chemotherapy; IT, immunotherapy; PD-1, programmed cell death protein 1; PD-L1, Programmed cell death 1 ligand 1; CTLA-4, cytotoxic T-lymphocyte-associated protein 4; OS, overall survival.

Table 2 Impact of smoking on each therapy

Therapy	Impact of smoking	Mechanisms/evidence	Implications
Immunotherapy	Generally effective in both smokers and non-smokers. Smokers may exhibit initially favorable responses due to higher TMB and greater PD-L1 expression. Some studies note reduced long-term survival in active smokers, possibly from altered drug metabolism and persistent immune dysfunction	Meta-analyses show both current and former smokers can benefit (HR -0.73-0.79). Higher TMB and PD-L1 are often found in smokers' tumors, leading to increased immunogenicity. Chronic inflammation and enzyme induction can reduce the durability of benefit	Smoking cessation could improve long-term outcomes. Personalized immunotherapy approaches (e.g., dose adjustments, combined cessation programs) may increase efficacy. Further prospective trials needed to clarify optimal management for smokers
Targeted therapy	EGFR-TKIs (e.g., erlotinib) are generally less effective in smokers vs. never-smokers. ALK inhibitors show somewhat less difference by smoking status. Smoking can increase drug clearance and facilitate resistance-related mutations	Smokers experience lower plasma levels of some EGFR-TKIs due to cytochrome P450 induction. T790M and other mutations occur more frequently in smokers, reducing EGFR-TKI response. ALK-rearranged tumors often maintain sensitivity regardless of smoking status	May require dosage adjustments for EGFR-TKIs in smokers. Molecular profiling and smoking history should guide therapy selection. Emphasizes need for next-generation inhibitors to overcome acquired resistance

A narrative review

Yang et al,
Transl Cancer Res 2025

Conclusions

- Oncogene addiction is far more frequent in NSs vs ESs.
- Oncogene-addicted NSCLC is generally sensitive to targeted therapies and smoking status has a limited role in the prediction of benefit.
- A different history is to be told about immunotherapy: smokers have higher ORRs with IT, but all-cause mortality is much higher than NSs.
- **Smoking status has an impact on pts'survival. Smoking cessation is to be pursued in pts with cancer, since it has a primary role in long-term outcomes, sometimes higher than some therapies!**