Association Between Smoking History and Overall Survival in Patients Receiving Pembrolizumab for First-Line Treatment of Advanced Non–Small Cell Lung Cancer

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JAMA Network Open. 2022;5(5):e2214046. doi:10.1001/jamanetworkopen.2022.14046

Question ?

Is smoking status associated with overall survival among patients with advanced non–small cell lung cancer (NSCLC) treated with first-line (1L) pembrolizumab monotherapy in a clinical setting?

Why this study ?

With the development and proven role of immunotherapy in different cancers, there is a constant urge to find out a predictive markers (Clinical or lab based or combination of both).

So that we can find the group of patients, who will benefit from chemotherapy as compared to the whole cohort.

As PDL1 alone is not able to predict the response, we are trying to look for further clinical markers and try to incorporate them to take a better decision.

Objective

To compare overall survival (OS) between patients with a current or former history of smoking with patients who never smoked and initiated **pembrolizumab monotherapy as first-line** (1L) treatment for advanced non–small lung cancer (NSCLC).

Material n Methods

- Retrospective study
- Nationwide (US) real world data
- January 2011 to Oct 2019
- 280 US clinics
- > 18 year with advanced stage NSCLC

- Smoking status at diagnosis of NSCLC

- OS measured from initiation of 1st line Pembrolizumab monotherapy

Demography

- 1166 patients

•Exclusion –

- Driver mutation positive
- > 90 days from diagnosis to treatment
- < 6 months follow up – to account for the COVID pandemic

•End point of interest – OS

•IPTW – To adjust for difference in patient characterstics between smokers and non smokers – Inverse probability treatment weighing was used.

Table. Baseline Patient Characteristics Before and After IPTW Adjustment of the Primary Analysis[a]

Characteristic	Unadjusted, No. (%)		SMD	Post-IPTW adjustment, No. (%)		SMD
	Never-smokers	Ever-smokers		Never-smokers	Ever-smokers	
Sample size (unadjusted)	91	1075	NA			
ESS (post-IPTW adjustment)				60	1072	NA
Age, <65	12 (13.2)	301 (28.0)	0.37	23.4 (26.1)	288.6 (26.8)	0.02
Sex						
Female	61 (67.0)	524 (48.7)	0.38	43.4 (48.3)	539.3 (50.2)	0.04
Male	30 (33.0)	551 (51.3)		46.5 (51.7)	535.7 (49.8)	
Race						
White	61 (67.0)	790 (73.5)	0.15	57.8 (64.1)	791.2 (73.6)	0.21[c]
Other races[b]	21 (23.1)	192 (17.9)		21.7 (24.2)	190.4 (17.7)	
Unknown	9 (9.9)	93 (8.7)		10.5 (11.7)	93.5 (8.7)	
Histology						
Nonsquamous	70 (76.9)	738 (68.7)	0.21	61.9 (68.9)	744.9 (69.3)	0.01
Squamous	17 (18.7)	294 (27.3)		24.3 (27.1)	286.8 (26.7)	
Not otherwise specified	4 (4.4)	43 (4.0)		3.8 (4.0)	43.4 (4.0)	
Cancer stage at diagnosis						
Stage I-III	25 (27.5)	372 (34.6)	0.16	28.6 (31.8)	365.7 (34.0)	0.05
Stage IV	66 (72.5)	703 (65.4)		61.3 (68.2)	709.4 (66.0)	
ECOG						
0	30 (33.0)	251 (23.3)	0.29	21.3 (23.7)	258.9 (24.1)	0.12[c]
1	42 (46.2)	477 (44.4)		44.9 (50.0)	478.9 (44.6)	
≥2	19 (20.9)	347 (32.3)		23.7 (26.3)	337.2 (31.4)	
Time since diagnosis, median (range), mo	0.89 (0.28-4.32)	0.95 (0-5.01)	0.14	0.92 (0.28-4.32)	0.95 (0-5.01)	0.07
No. of sites of metastases, median (range)	0 (0-2)	0 (0-3)	0.01	0 (0-2)	0 (0-3)	0.05
CNS metastases, none	2 (18.2)	48 (29.3)	0.26	1.9 (17.8)	48.1 (29.5)	0.28[c]
Liver metastases, none	88 (96.7)	1026 (95.4)	0.07	87.2 (97)	1026.3 (95.5)	0.08
Lung metastases, none	88 (96.7)	1045 (97.2)	0.03	87.3 (97.1)	1045.0 (97.2)	0.01
Other metastases, none	73 (80.2)	841 (78.2)	0.05	73.0 (81.2)	840.9 (78.2)	0.07
Recorded PD-L1 positivity, absent	24 (26.4)	229 (21.3)	0.12	20.2 (22.5)	233.3 (21.7)	0.02
Insurance status, insured	66 (72.5)	787 (73.2)	0.02	66.8 (74.3)	786.3 (73.1)	0.03
Practice type						
Academic	9 (9.9)	109 (10.1)	0.01	9.5 (10.6)	109.7 (10.2)	0.01
Community	82 (90.1)	966 (89.9)		80.3 (89.4)	965.3 (89.8)	

Results

- 8 % Non smokers

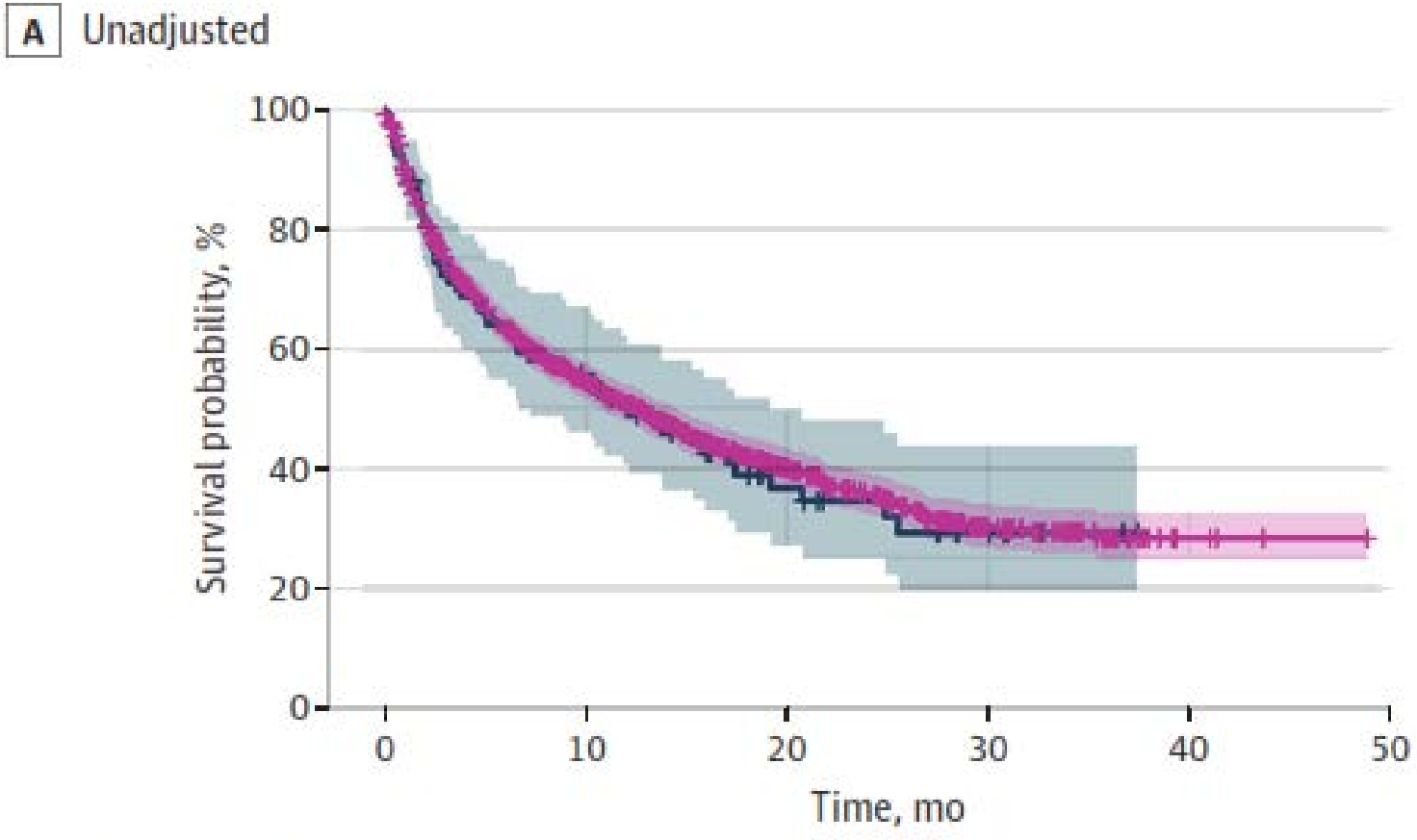
- Non smokers were
- Older – Median age – 78.2 vs 72.7 yrs
- Females – 67 % vs 49 %
- Non squamous histology – 77 % vs 68.7 %

Results

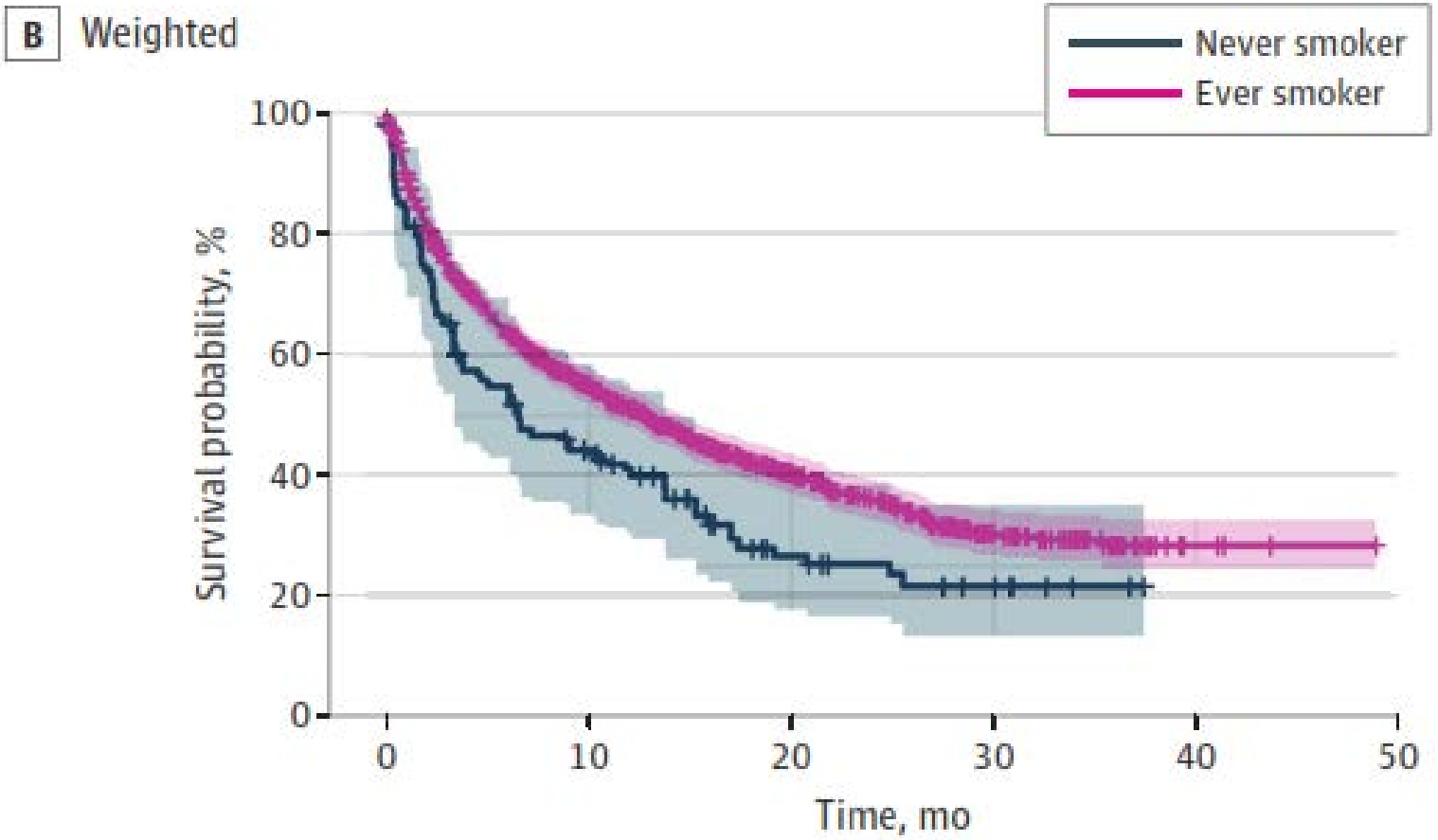
- No adjustment of baseline cavariates –
- OS for ever smoker = non smokers
- 12.1 month vs 12.5 month

- After covariates adjustment –
- Ever smokers have a significant longer OS than never smokers.
- 12.8 months vs 6.5 months

Kaplan-Meier curve for NS n ES – 1st line Pembrolizumab monotherapy Unadjusted comparison



Kaplan-Meier curve for NS n ES – 1st line Pembrolizumab monotherapy Adjusted comparison



Discussion - TMB

TMB (47). TMB is another widely accepted biomarker for predicting the immunotherapy response among patients (48). It is widely acknowledged that NSCLC and melanoma are the two cancer types that most benefit from immunotherapy, and this has largely been attributed to the high TBM in both cancer types (49). While ultraviolet exposure is the major cause of DNA damage and elevated TMB in melanoma as a skin cancer, tobacco exposure likely contributes to the high TMB in lung cancer. A previous study showed that lung cancers in smokers had a significantly higher TMB compared with lung cancers in never-smokers (49). A high TMB contributes to the production of a higher abundance of neoantigens, which facilitates the recognition of cancerous cells by the immune system. Also, accumulation of neoantigens on the surface of tumor cells can stimulate the recruitment of cytotoxic immune cells into the tumor microenvironment, which will further boost the therapeutic efficacy of immunotherapy.

Discussion – Tumor Micro environment

chronic obstructive pulmonary disease, smoking is thought to play a role in skewing the local immune microenvironment to a proinflammatory phenotype (50). Previous studies have also reported that the immunologic homeostasis within the tumor microenvironment is less compromised in never-smokers compared with ever-smokers (51, 52). It is believed that immune cells are recruited in response to tobacco exposure, in an attempt to minimize the damage induced by the carcinogenic substance *via* a pro-inflammatory reaction (53). However, the immune cells could also partially contribute to the harmful tumor microenvironment that promotes tumor growth (54). Smoking can influence the tumor microenvironment not only during the stage of tumor initiation, but may continue its effect throughout the process of tumor progression. For example, tobacco exposure was reported to polarize macrophages to a proinflammatory phenotype, M1 (55).

Discussion - Oncogenic mutations

- EGFR, ALK, ROS 1 being more common in non-smokers. – Respond poorly to Immunotherapy.

- KRAS being more common in smokers.
- Data suggest that patients having KRAS mutation respond better to immunitherapy.

- PD L1 – Higher expression in smokers.

Other data

Open access Original research

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Tobacco smoking and cessation and PD-L1 inhibitors in non-small cell lung cancer (NSCLC): a review of the literature

Jan Norum,[1] Carsten Nieder[2]

To cite: Norum J, Nieder C. Tobacco smoking and cessation and PD-L1 inhibitors in non-small cell lung cancer (NSCLC): a review of the literature. *ESMO Open* 2018;**3**:e000406. doi:10.1136/esmoopen-2018-000406

Received 23 May 2018
Revised 6 August 2018
Accepted 7 August 2018

ABSTRACT

Background Programmed death ligand 1 (PD-L1) targeting immunotherapies, as pembrolizumab and nivolumab, have significantly improved outcome in patients with non-small cell lung cancer (NSCLC). Tobacco smoking is the number one risk factor for lung cancer and is linked to 80%–90% of these cancers. Smoking during cancer therapy may influence on radiotherapy and chemotherapy outcome. We aimed to review the knowledge in immunotherapy.

Patients and methods A systematic review was done. We searched for documents and articles published in English language and registered in Cochrane Library, National Health Service (NHS) Centre for Reviews and Dissemination (CRD), Embase or Medline. The search terms were (A) (Lung cancer or NSCLC) with (pembrolizumab or nivolumab) with PD-L1 with (tobacco or smoking) and (B) Lung Neoplasms and Immunotherapy and (smoking cessation or patient compliance). 68 papers were detected and two more were added during review process (references) and six based on information from the

Key questions

What is already known about this subject?

- Tobacco smoking is the number one risk factor for lung cancer and is linked to 80%–90% of these cancers.
- Studies have indicated the mutation burden associated with smoking predicts response to immunotherapy. This is due to a higher programmed death ligand 1 (PD-L1) tumour proportion score (TPS) among smokers.

What does this study add?

- There is a better overall response rate among the current/former smoker group than the no smoker group when treated with immunotherapies. So also in patients having a molecular 'smoking signature'. This is due to a higher PD-L1 TPS and probably a higher mutational burden due to smoking.
- The situation seems to be different during therapy. The KEYNOTE-024 documented pembrolizumab

Other data

Received: 11 December 2020 | Accepted: 6 January 2021

DOI: 10.1111/1759-7714.13852

ORIGINAL ARTICLE

WILEY

Smoking status during first-line immunotherapy and chemotherapy in NSCLC patients: A case–control matched analysis from a large multicenter study

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Other data

Mo et al. World Journal of Surgical Oncology (2020) 18:15
https://doi.org/10.1186/s12957-020-1792-4

World Journal of Surgical Oncology

REVIEW Open Access

Smokers or non-smokers: who benefits more from immune checkpoint inhibitors in treatment of malignancies? An up-to-date meta-analysis

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Abstract

Background: Immune checkpoint inhibitors, which are a milestone in anti-cancer therapy, have been applied in the treatment of multiple malignancies. Real-world data have suggested that smoking status may be associated with the efficacy of anti-PD-1/PD-L1 therapy. Hereby, to evaluate "smoking benefit or not", we included numerous high-quality randomized controlled clinical trials (RCTs) without any restriction on category.

Methods: A systematic search of online database was performed from July 2010 to July 2019. Eligible studies included phase II/III RCTs comparing PD-1/PD-L1 inhibitors with chemotherapy in the treatment of multiple carcinomas and contained subgroup analysis of smoking status. Then, related hazard ratios (HRs) with 95% confidence intervals (CIs) of overall survival (OS) were pooled.

Results: In the initial meta-analysis, compared with chemotherapy, the OS of non-smokers (HR, 0.81; 95% CI, 0.67–0.98) and smokers (HR, 0.77; 95% CI, 0.71–0.83) were significantly prolonged with PD-1/PD-L1 inhibitors. Outcomes from subgroup analysis showed that in anti-PD-1/PD-L1 monotherapy groups, non-smokers showed no significant improvement in OS (HR, 0.94; 95% CI, 0.83–1.06), while the OS of smokers was significantly prolonged (HR, 0.79; 95% CI, 0.74–0.85); in groups of PD-1/PD-L1 inhibitors combined with chemotherapy, the OS of non-smokers (HR, 0.45;

Crux

- There is multiple data available of added benefit of Immunotherapy in Smokers as compared to non-smokers.

- We need to rise above the individual markers like PDL1, TMB, MSI, Clinical parameters and should decide on coming up with a combined flowchart or formula to look for that which patients will not benefit from immunotherapy, so that we can omit immunotherapy in those.

Thank You.