



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

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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 manufacturers.

Results Nine papers were selected. High PD-L1 expression ($\geq 50\%$) was correlated with current/ever smoking history in three studies. Six studies revealed a higher overall response rate (ORR) among current/former smokers. The ORR was generally (six studies) better among the current/former smoker group. So also when tumours had a molecular ‘smoking signature’ (one study). This was probably due to a higher mutational burden. In two studies, minor or no difference was revealed.

One study (KEYNOTE-024) compared former and current smokers, and documented pembrolizumab being more effective among former smokers than current smokers.

Conclusions Tobacco smoking patients with NSCLC generally have a higher PD-L1 tumour proportion score and experience a better ORR of immunotherapy than no smokers. There is little evidence on the effect of smoking during immunotherapy, but one study (KEYNOTE-024) may indicate survival gains of smoking cessation.

INTRODUCTION

Cigarette smoking is the number one risk factor for lung cancer and is linked to about 80%–90% of lung cancers.¹ There are more than 4000 chemical constituents of cigarette smoke and there are several potential

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 being more effective among former smokers than among current smokers.

How might this impact on clinical practice?

- ▶ Clinicians may encourage patients undergoing immunotherapy to quit smoking to achieve a better outcome.
- ▶ There is a need to clarify the benefit achieved. When elucidated, more pressure can be put on patients continuing smoking during therapy. They may cause waste of healthcare resources spent on their therapy.

carcinogens, including polycyclic aromatic hydrocarbons, aromatic amines, nitrosamines and other organic and inorganic compounds, such as benzene, vinyl chloride, arsenic and chromium. The carcinogens are associated with DNA mutations. Lung cancer accounts for 21% of the total cancer deaths worldwide.¹ Every year, 1.8 million people are diagnosed with lung cancer, and 1.6 million people die because of the disease. In the USA, lung cancer represents almost 27% of

all cancer deaths.² Five-year survival rates vary from 4% to 17%, depending on stage and regional differences.³

Rates have been declining due to the reduced prevalence of smoking. However, in the USA, 18% of adults still smoke cigarettes.^{2,4} A similar figure (19%) has been reported in Norway.⁵ The declining rates have, however, been absent in several economically low/middle-income countries.¹

Today, lung cancer from smoking is, to a great extent, a preventable disease.⁶ A 62% reduction in lung cancer mortality has been reported in association with smoking cessation at age 50.⁷ Quitting smoking decreases the risk of dying from lung cancer and from other tobacco-related illnesses. Consequently, programmes and policies that can decrease the numbers of tobacco smokers will have significant impact on patients' quality of life and healthcare budgets.⁷

During the last years, new costly drugs have been introduced for the treatment of lung cancer.⁸ Examples of inhibitory signalling agents approved by the Food and Drug Administration include antibodies targeting cytotoxic T-lymphocyte-associated protein 4 and programmed death 1 (PD-1)/PD-ligand 1 (L1) receptors.⁹ Especially, PD-1/PD-L1 blockage therapy has shown activity in lung cancer.¹⁰⁻¹² Economic resources spent on costly new therapies could be allocated to preventive strategies. Treatment effects in various subgroups should therefore be monitored.

Smoking can cause lung cancer and then block the body from fighting it by weakening the immune system.¹³ Tobacco smoking during immunotherapy may influence on treatment outcome. Progression-free survival (PFS) has been documented varying, depending on whether the patient was a former or current smoker.¹⁴ Furthermore, the mutation burden associated with smoking may predict response to anti-PD-1 therapy.¹⁵ In this review, we aimed to clarify the consequences of tobacco smoking before and during immunotherapy.

MATERIALS AND METHODS

We performed a systematic literature search for studies on immunotherapies in lung cancer and possible effects of tobacco smoking. In February 2018, we searched for documents and articles published in English language. The following databases were used: Cochrane Library, National Health Service (NHS) Centre for Reviews and Dissemination (CRD), Embase and Medline. The following search terms were used: (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). A total of 68 papers were detected.

Initially, we screened all titles and abstracts of the articles. The selected papers were investigated and studies reporting any analysis on correlation between smoking and immunotherapy were selected (n=7). Furthermore, the references of the selected papers were screened and another two articles were added.^{14 16}

Merck Sharp & Dohme, the manufacturer of pembrolizumab (Keytruda), Bristol Myers Squibb, the manufacturer of nivolumab (Opdivo), and Roche, the manufacturer of atezolizumab (Tecentriq) were contacted and requested for information concerning tobacco smoking and the treatment of non-small cell lung cancer (NSCLC) using pembrolizumab, nivolumab or atezolizumab. They confirmed several of the selected articles, and two more articles and four abstracts were added for further analyses.¹⁷⁻²²

Because of low level of evidence, abstracts only, book chapters, errata, editorial comments and letters to the editor were not included. Consequently, six papers (published as abstracts only) were excluded. Furthermore, articles were excluded when they did not focus on lung cancer, immunotherapy or the use of tobacco, and/or not written in English language (61 articles rejected). We reviewed the full text of all articles twice to confirm their eligibility. Following the selection process, nine articles were included into the final study.^{14-18 23-26} Data were extracted from the selected papers employing Microsoft Excel V.2016 for the database. Never smoking was defined as patients who had smoked less than 100 cigarettes in their lifetime or ≤ 10 package-years.^{24 26} Study characteristics, treatment, comparator and numbers are given in table 1.

RESULTS

Literature search

The literature selection process revealed nine studies fulfilling the inclusion criteria and reporting data on tobacco use, PD-L1 expression and response on immunotherapy in NSCLC. The selection process and key findings are shown in figure 1 and table 1.

Smoking before immunotherapy

Smoking history and its influence on the effect of immunotherapy was somewhat diverging. In three studies, high PD-L1 expression ($\geq 50\%$) was correlated with current/ever smoking history.²⁴⁻²⁶ Gainor *et al* documented in their retrospective study (58 patients) a better (but not significant, $p=0.123$) overall response rate (ORR) among heavy smokers versus never or light smokers.²⁴ The figures were 20.6% and 4.2%, respectively. Garon and colleagues published, on behalf of the KEYNOTE-001 investigators, that current or former smoking status was associated with an increased response to treatment.¹⁶ They concluded this finding was probably due to a higher mutational burden among these patients. The median PFS among current/former smokers was 4.2 months vs 2.1 months among the never smokers. The corresponding overall survival (OS) figures were 14.3 and 8.8 months, respectively.

Gandhi and associates added pembrolizumab or placebo to pemetrexed and a platinum-based regimen in first-line therapy of patients with advanced NSCLC.¹⁷ Most patients (88.1%) were former or current smokers. They revealed an HR for OS of 0.23 (95% CI 0.10 to 0.54) for

Table 1 An overview of the study characteristics, treatment and comparator, type of evaluation, perspective, year of value and time horizon of the selected studies

Reference	Study characteristics	Treatment and comparator	n	Key findings
24	Patients with NSCLC treated with nivolumab	Nivolumab monotherapy	50	Response to treatment before nivolumab associated with response to nivolumab. Smoking history had no significant influence (never vs current/former smoker ORR 5% vs 26%, $p=0.1269$).
16	Sequenced exons of NSCLCs	Pembrolizumab	34	Efficacy greater in tumours harbouring smoking signature (ORR 56% vs 17%, $p=0.03$)
25	EGFR and ALK rearrangements in NSCLC	PD-1/PD-L1 inhibitors	58	Smoking history had no significant influence (never/light vs heavy smokers ORR 4.2% vs 20.6%, $p=0.123$).
26	Adenocarcinoma of the lung	Testing PD-L1 tumour proportion score	71	Tumours with a PD-L1 TPS>50% were significantly associated with smoking status.
27	Patients with NSCLC in East Asia. 108 SCC and 221 LUAD.	PD-L1 expression/distribution	329	TPS>50% correlated with smoking history in both SCC ($p=0.008$) and adenocarcinoma ($p=0.002$).
17	Pembrolizumab in NSCLC. KEYNOTE-001.	Pembrolizumab 10 mg/kg every 2 weeks, 2 mg/kg every 3 weeks, 10 mg/kg every 3 weeks	495	Current/former smoking status was associated with increased ORR (10.3% vs 22.5% in never smokers).
15	Pembrolizumab or platinum-based CT. KEYNOTE-024.	Pembrolizumab 200 mg every 3 weeks Platinum	305	ORR 44.8% vs 27.8%. HR for progression/death among smokers 0.68 and former smokers 0.47.
18	Pemetrexed and platinum plus pembrolizumab or placebo in advanced NSCLC. KEYNOTE-189.	Pemetrexed, platinum and pembrolizumab or placebo every 3 weeks	616	88.1% current or former smokers. HR for death among current or former smokers 0.54 versus never smoker 0.23. Progression-free survival HR 0.54 and 0.43, respectively.
19	Nivolumab versus docetaxel in patients with NSCLC. Phase III study.	Nivolumab 3 mg/kg every 2 weeks versus docetaxel 75 mg/m ² every 3 weeks	582	79% were current/former smokers. HR was 0.70 and 1.02 in former/current smokers and never smokers, respectively.

ALK, anaplastic lymphoma receptor tyrosine kinase; CT, chemotherapy; EGFR, epidermal growth factor receptor; LUAD, lung adenocarcinoma; NSCLC, non-small cell lung cancer; ORR, overall response rate; PD-L1, programmed death ligand 1; SCC, squamous cell carcinoma; TPS, tumour proportion score.

never smokers and 0.54 (95% CI 0.41 to 0.71) for current/former smokers. The corresponding figures for disease progression or death were 0.43 (95% CI 0.23 to 0.81) and 0.54 (95% CI 0.43 to 0.66), respectively. However, there were only 73 never smokers among 616 patients, causing a wide CI. The data cut-off was 8 November 2017.

Borghaei and colleagues compared nivolumab and docetaxel in 582 patients with advanced non-squamous NSCLC and concluded an OS benefit in favour of nivolumab (12.2 months vs 9.4 months).¹⁸ A total of 79% were current or former smokers. When comparing OS between current/former smokers versus never smoked, they revealed smokers having a greater benefit of nivolumab therapy. The unstratified HRs (95% CI) were 0.70 (95% CI 0.56 to 0.86) vs 1.02 (95% CI 0.64 to 1.61), respectively. However, the interpretation of the results

was somewhat limited by the wide CI in a small subgroup of patients (118 out of 582 had never smoked).

Based on the majority of studies, we concluded, there is a correlation between smoking history and higher PD-L1 tumour proportion score.^{16 18 25 26}

Molecular signature of smoking and immunotherapy

Rizvi and colleagues identified the molecular signature of smoking to clarify the efficacy of pembrolizumab in patients with NSCLCs harbouring the smoking signature.¹⁵ A previously validated binary classifier was applied.²⁷ The ORR was significantly higher in tumours with smoking signature versus never smoking signature (56% vs 17%, $p=0.03$).¹⁵ Similar findings were detected in PFS with median survival not reached versus 3.5 months ($p=0.0001$). Whereas smoking signature significantly correlated with efficacy, self-reported smoking status

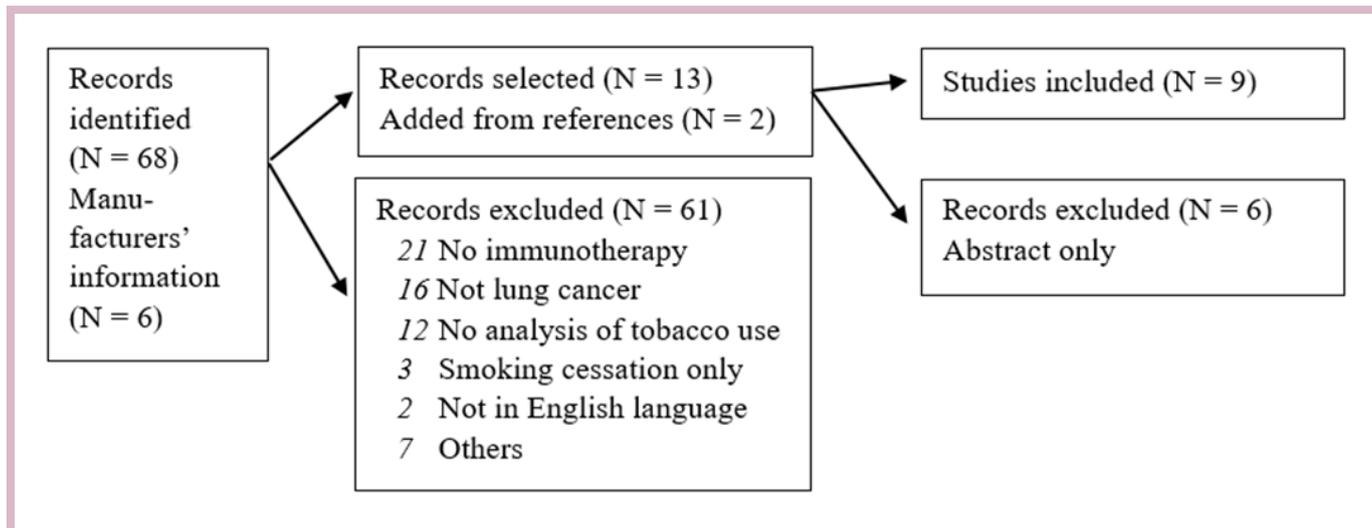


Figure 1 The selection process.

did not. Kobayashi *et al* did also conclude similarly.²³ In their study, smoking history (never vs current or former smoker) did not influence on response rate of nivolumab monotherapy, but the study included only 50 patients and 31 out of them were current smoker or ever smoker.

Smoking during immunotherapy

There was only one study comparing former smokers with current smokers.¹⁴ The categorisation was based on patients' smoking status at study entry and the investigators documented a better effect of pembrolizumab therapy among former smokers (216 patients) compared with current smokers (65 patients). The HRs for disease progression or death were for current smokers 0.68 (95% CI 0.17 to 0.71) and for former smokers 0.47 (95% CI 0.33 to 0.67). Brahmer *et al* updated these data (data cut-off 10 July 2017) in an abstract version.²⁸ The paper indicated a better response among those being former smokers at the initiation of immunotherapy. No study compared smoking habits in terms of whether the patient actually stopped smoking or continued during immunotherapy.

DISCUSSION

We conclude most studies revealed a correlation between tobacco smoking and higher PD-L1 tumour proportion score. This was probably due to a higher mutational burden. There was little evidence on the effect of tobacco smoking during immunotherapy. However, one major study revealed better outcome for former smokers than for the current ones.¹⁴ This indicates that smoking cessation should be encouraged before and during immunotherapy.

Smoking status, response rate and survival

Some discrepancy between studies may be due to various numbers of patients and the fact that smoking status was based on patients' self-reports.^{15 23 24} There were no follow-ups and none of the studies did actually measure

blood level of nicotine and no studies did split data between former and current smokers.²⁹ Consequently, there is a need for studies on the possible effect of continuing smoking during immunotherapy.

Smoking status among patients with NSCLC has been reported varying between real world and clinical trials.³⁰ However, we could not confirm this statement. Khozin *et al* mentioned a real-world current/former smoker figure (88%) similar to that of the KEYNOTE-024 study (92%).^{14 30} Similar figures have also been reported by others (79%–88%).^{17 18}

The proportion score of PD-L1 expression of at least 50% was associated with a higher ORR, and longer PFS and OS.³¹ This effect was hypothesised to be due to a higher mutational burden.^{32–34} Consequently, differences in ORR between various studies might be due to variations in the percentage of smokers. This was also argued by Kobayashi *et al*.²³

In our review, most data were on pembrolizumab and nivolumab. However, other drugs have also been tested and data published in abstract forms. Such an example is the MPDL3280A.³⁵ This is an engineered IgG anti-PD-L1 antibody with modified Fc domain that prevents antibody-dependent cell-mediated cytotoxicity in other immune cells expressing PD-L1. The MPDL3280A achieved a better ORR among former and current smokers (25%) than among never smokers (16%).³⁵ This was also confirmed by others.³⁶

Pneumonitis is one of the potentially serious side effects of immunotherapy. Ahn and colleagues reported pneumonitis grades 3–5 in 3.8% of patients with NSCLC undergoing pembrolizumab therapy.³⁷ Smoking history did however not influence the risk of pneumonitis. Leighl *et al* recently published an abstract updating the KEYNOTE-001 study.¹⁹ Three years of survival in previously treated patients was better among ever (21.9%; 95% CI 17.1 to 27.2) than never (11.9%; 95% CI 6.3 to 19.5) smokers. Looking at treatment-naïve patients, the 3 years of OS was

in favour of those who had never smoked (24.0%; 95% CI 11.7 to 38.7 vs 45.5%; 95% CI 16.7 to 70.7). Consequently, the never smoked group seems to have the best prognosis in the treatment-naïve setting. However, the number of patients and the number of adverse events were too small to draw any conclusions.

Molecular signature and immunotherapy

Rizvi and colleagues employed a previously validated binary classifier to identify the molecular signature of smoking.^{15, 27} The classifier applied differentiated transversion-high (smoking signature) from transversion-low (never smoking signature) tumours.²⁷ This classification was based on the fact that past or present smoking has been shown to be associated with cytosine to adenine (C>A) nucleotide transversions both in individual genes and genomic-wide.³⁸ Furthermore, the C>A nucleotide transversion has been shown inversely correlated with cytosine to thymidine (C>T) transition frequency.^{38, 39}

It could be questioned whether smoker tumours should be defined by the genetic signature rather than by self-reported smoking status. However, we did not reveal large-scale studies that could answer this question and the study by Rizvi *et al* did only include 30 patients.¹⁵

On the other hand, we revealed one study showing a correlation between amounts of smoking and genetic alterations.⁴⁰ The puff volume was indicated a more powerful objective phenotype of smoking behaviour than self-reported cigarettes per day and nicotine dependence.

Should patients quit smoking during immunotherapy?

Patients frequently ask what they can do themselves to improve treatment outcome. Smoking cessation may be a key action in this setting.⁴¹ Smoking not only causes cancer, but continued smoking may alter cancer biology, leading to tumours that are resistant to treatment and thereby increase mortality.⁴² Smoking cessation may also improve cardiovascular status. Consequently, we argue that oncologists and pulmonologists should encourage smoking cessation during immunotherapy.

O'Malley and colleagues did a review of the literature on metabolism and effectiveness of systemic therapy for lung cancer.⁴³ They revealed that smokers might exhibit a more rapid clearance, requiring a higher dose compared with non-smokers. However, no studies have shown the influence of continuous smoking on the clearance of immunotherapies. A detailed smoking history should be part of future clinical evaluations in NSCLC. At least three levels of smoking status should be ascertained (never smoker, former smoker and current smoker) and the number of pack-years should be calculated.

Smoking cessation is not easy and the success rate has been disappointing.⁴⁴ Therefore, patients should be offered assistance during and after smoking cessation.⁴⁵

CONCLUSION

Tobacco smoking patients with NSCLC generally have a higher PD-L1 tumour proportion score and

experience a higher response rate in immunotherapy than non-smokers. There is little evidence on the effect of smoking during immunotherapy, but one study indicates better outcome for former smokers than for the current ones. Further studies are necessary to elucidate the negative effects of smoking during immunotherapy.

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