# Anti-PD-1/PD-L1 to CTLA-4

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cancer clinical predictor drug hazard ratio lung smoking

## 1. Introduction

Traditionally, it has been recognized that smoking increases the risk for enhanced disease progression and affects the efficacy of treatment in patients with non-small cell lung cancer (NSCLC). Data from the Centers for Disease Control and Prevention (CDC) show that smoking is linked to about 80% to 90% of lung cancers (https://www.cdc.gov/cancer/lung/basic_info/risk_factors.htm, accessed on 22 April 2020). In a prior analysis of patients treated for NSCLC, we found that non-smokers had a lower risk of 0·16 HR compared to those who had ever smoked, with only a single study demonstrating conflicting results [1]. However, recent results from several large clinical trials of programmed death-1 (PD-1) and programmed death-ligand 1 (PD-L1) inhibitors showed that smokers had lower HR values than non-smokers [2][3][4][5]. Wallis et al. (2019), while conducting a meta-analysis on the association between smoking and survival of patients having benefited from immunotherapy in advanced malignancies, concluded that there was no difference between smokers and non-smokers in response to immunotherapy. In the same sense, Mo et al. (2020) reported that smokers benefited from either anti-PD-1/PD-L1 monotherapy or the combined regimen compared with chemotherapy. These contrasting data raise the question of the mechanism underlying the differential response of smokers treated with PD-1/PD-L1 and potentially other immunotherapy drugs.

PD-1 is an important factor in the normal immune response to prevent autoimmunity. Currently, clinical trials have reported results from five drugs in this category: two anti-PD-1 drugs (Nivolumab and Pembrolizumab) and three anti-PD-L1 drugs (Atezolizumab, Durvalumab, and Avelumab). Nivolumab, a fully humanized monoclonal antibody against PD-1, has shown a survival benefit in a number of cancers, including malignant melanoma [6], NSCLC [7], advanced renal cell carcinoma [8], and other types of cancers [9]. Pembrolizumab was the first anti-PD-1 antibody to be approved by the US Food and Drug Administration (FDA) for the treatment of patients with unresectable or metastatic melanoma with disease progression following Ipilimumab. It has also been used for the treatment of NSCLC [10] and other cancers. Atezolizumab is a PD-L1 inhibitor used in cancer therapy with a focus on bladder and NSCLC [11]. Durvalumab is reported as a selective, high-affinity, human IgG1 monoclonal antibody that blocks PD-L1. It has been used for the treatment of NSCLC [12] and urothelial carcinoma [13]. Avelumab is a promising new therapeutic agent for patients with metastatic Merkel cell carcinoma that has also been used in the treatment of NSCLC [14].

CTLA-4 is the second molecule of the immune checkpoint that has been targeted by monoclonal drugs [15]. Data on the status of smokers in response to the anti-CTLA-4 drug treatment are available. The anti-CTLA drug, Ipilimumab was efficient intreating NSCLC [16][17]. Both anti-PD-1/PD-L1 and CTLA-4 are also cell surface molecules [16][17][18][19][20][21]. The question is whether smokers respond better to both checkpoint drugs and their combination.

## 2. Smoking as a Favorite Predictor for Drugs of Anti PD-1/PD-L1, MUC1, CTLA-4

The effects of smoking on treatment outcome data were analyzed with a meta-analysis for two major categories of drugs, immune checkpoint inhibitors (anti-PD-1/PD-L1 and CTLA-4 drugs) and other drugs including MUC1, EGFR, and angiogenesis inhibitors. Diseases treated with anti-PD-1 and anti-PD-L1 drugs included NSCLC and other types of cancers. Data analyzed for other drugs were only from NSCLC patients. To examine the effect of only anti-PD-1 and anti-PD-L1, within the data of anti-PD-1 and anti-PD-L1 drugs, a sub-group analysis was conducted based on the treatment matrix, including monotherapy versus combination treatment and maintenance therapy. To examine the effect of combination between anti-PD-1/PD-L1 and CTLA-4 drugs, patients' responses to the combination treatment between drugs from these two types of checkpoint drugs were analyzed.

Our review is based on published results from clinical trials from PubMed, PMC/MEDLINE, and Scopus. Inclusion criteria were reported in clinical trials with different smoking statuses. **Table 1** shows data from a set of 36 clinical trials including 13 on NSCLC and 6 on other cancers treated with PD-1/PD-L1 drugs, 5 on cancer patients treated with anti-CTLA-4 drugs, 2 treated with anti-MUC1 drugs, and 10 with anti-VEGF drugs.

**Table 1.** Additional data collected from clinical trials.

| Drugs/First Author | Drug Comparison | Subgroup Analysis | Current/# Patients | Former/# Patients | Never/# Patients | Overall/# Patients | Note |
|---|---|---|---|---|---|---|---|
| Pembrolizumab/Shaverdian (50) | KEYNOTE-001 phase 1 trial Former smokers vs non-smokers | Progression-free survival (PFS) | | 0.60 (0.38–0.95) vs. 1 * | | | |
| | | Any previous radiotherapy and PFS | | 0.78 (0.47–1.31) vs. 1 * | | | |
| | | Previous extracranial radiotherapy and PFS | | 0.82 (0.49–1.37) vs. 1 * | | | |
| Pembrolizumab/Reck (51) | Update on KEYNOTE-024 | Subgroup analysis of overall | 0.81 (0.41–1.60)/65 | 0.59 (0.41–0.85)/216 | 0.90 (0.11–7.59)/24 | 0.63 (0.47–0.86)/305 | All are PD-L1 expression |

| Drugs/First Author | Drug Comparison | Subgroup Analysis | Current/# Patients | Former/# Patients | Never/# Patients | Overall/# Patients | Note |
|---|---|---|---|---|---|---|---|
| | vs. Chemotherapy | survival (OS) | | | | | on at least 50% of tumor cells |
| Nivolumab/Lee (52) | To patients failed prior platinum-based chemotherapy | Objective response rates | 15/78 (19.2) | | 5/22 (22.7) | | PD-L1 status not known. |
| Nivoluma/Dumenil (37) | Prospectively and treated by nivolumab in two French academic hospitals | PFS | 1 (1.00–1.00) * | 0.85(0.45–1.58) | 1.93 (0.79–4.68) | | Previously not included because of patients less than 100 |
| | | OS | 1 (1.00–1.00) * | 1.09 (0.58–2.05) | 2.15 (0.89–5.22) | | |
| Durvalumab/ Sridhar (Sridhar et al., 2019) | Study 1108/ durvalumab monotherapy | Adjusted HR for OS | Ever versus Never: 0.85 by Cox Proportional Hazards Model (Cox Model) | | | - | - |
| | | HR for | Ever versus Never: 0.85 (OS by Cox Model, Including PD-L1/LM Subgroups) | | | - | - |
| | | HR for PFS by | Ever versus Never: 0.66 (Cox Model, Including PD-L1/LM Subgroups) | | | - | - |
| | ATLANTIC /Durvalumab as third-line or later treatment (53) | Adjusted HR for OS | Ever versus Never: 1.67 (by Cox Model) | | | - | - |
| | | HR for OS | Ever versus Never: 1.67 (by Cox Model, Including PD-L1/LM Subgroups) | | | | |
| | | HR for PFS | Ever versus Never: 1.08 (by Cox Model, Including PD-L1/LM Subgroups) | | | - | - |

* Assumed values based on information from the study.

02; non-
ean HR values of smokers and non-smokers were 0.735 and 0.882, respectively. When we combined the anti-PD-1/PD-L1, anti-CTLA-4 drugs, and anti-MUC1 drugs, the mean HR values of smokers and non-smokers were 0.751 and 1.016, respectively. The *p*-values for comparison between smokers and non-smokers for data of three types of drugs, two types of drugs, and anti-PD-1/PD-L1 drugs only are 0.0325, 0.0299, and 0.0685, respectively (**Figure 1**A). The meta-analysis indicated that the smokers have an HR value of 0.023 lower than that of the non-smokers (**Figure 1**B) with heterogeneity of I2 = 0% and $p < 0.001$. In contrast, for anti-VEGF drugs, the mean HR value from the smoking subgroups in these trials was 0.868; the mean HR value from the non-smoking subgroup subgroups was 0.654, with a *p*-value of 0.0013 (**Figure 1**C). The meta-analysis indicated that the smokers have an HR value of 0.194 higher that of the non-smokers (**Figure 1**D), again with heterogeneity of I2 = 0% and $p < 0.001$. These data suggest a significant difference in the response to treatment between smokers and no-smokers when different drugs were used. Accordingly, a detailed description and subgroup and stratified meta-analysis were conducted to further analyze the difference between smokers and non-smokers for these drugs.

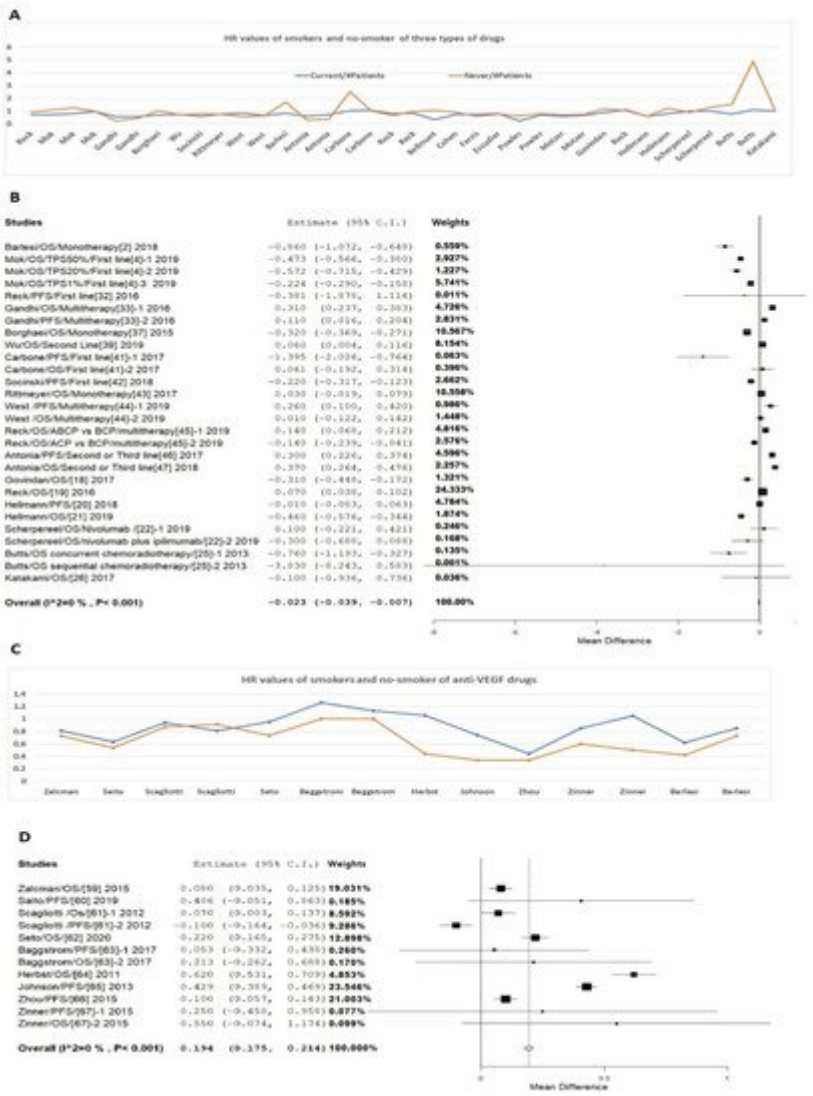


**Figure 1.** HR values of patients treated with different drugs. (**A**) HR data from three types of drugs (anti-PD-1/PD-L1, anti-CTLA-4 drug, and anti-MUC1 drug). (**B**) Meta-analysis of HR for these three types of drugs. (**C**) HR data from Bevacizumab on NSCLC between smokers and non-smokers. (**D**) Meta-analysis of HR Bevacizumab on NSCLC between smokers and non-smokers.

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