



# PD-1/PD-L1 inhibitors as a hope for smokers of non-small cell lung cancer patient

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We read with great interest the recent review article by Warren (1) on the adverse health effects and costs associated with smoking after a cancer diagnosis. We noticed Dr. Warren concluded that priority should be placed on interventions that reduce the effect of medication and associated costs caused by continued smoking after a cancer diagnosis. Dr. Warren also pointed out that research is desperately needed to ascertain if the adverse effects of smoking can be overcome with an existing or forthcoming cancer treatment. We wondered whether Dr. Warren noticed the recently reported clinical trials on the effects of drugs of programmed death-1 (PD-1) and programmed death-ligand 1 (PD-L1) inhibitors on non-small cell lung cancer (NSCLC), and whether Dr. Warrant could comment on the potential benefit of PD-1 and PD-L1 drugs to NSCLC patients who are still smoking.

First of all, we all know that smoking is harmful and greatly increases the risk of lung disease as has been confirmed many times over years of study. However, our question seeks to address the effect of smoking on treatment of lung cancer, i.e., how smoking lung cancer patients respond to treatment by variety of drugs. Smoking status has been analyzed in some but not all clinical trials of new drugs. Recent data from several clinical trials have indicated that it may be necessary to compare data on the effects of treatment among subgroups according to smoking status. We believe that future clinical trials should always include such analysis.

Smoking status of patients studied has been reported in the majority of large clinical trials. In the past, most of these results indicated that smoking negatively affects

treatment for cancer patients (2). However, the induction of lung cancer and the effects of cancer treatment are not the same. Different drugs have different mechanisms and affect different molecular pathways in different cancers. PD-1/PD-L1 inhibitors are relatively new types of drugs used in the treatment of cancer. Therefore response to treatment by PD-1/PD-L1 inhibitors should be carefully compared among patients differing in smoking status before any conclusions can be definitively reached.

In particular, two recent clinical trials of a PD-1 inhibitor in cancer patients reported that treatment by PD-1/PD-L1 inhibitors was more effective in smokers than non-smokers (3,4). In both publications the authors provided hazard ratio (HR) values as measured by median overall survival (OS) for patients from two different smoking status groups, the ever (smoker) and the never (smoker). In the report by Mok *et al.*, the authors analyzed the effect of pembrolizumab versus chemotherapy for previously untreated, PD-L1-expressing, locally advanced or metastatic NSCLC (3). Pembrolizumab is one of a family of PD-1/PD-L1 inhibitors. The authors reported response to treatment by patients having different smoking histories. In their three sub-group analyses, smokers had lower HR values than that the non-smokers in all of them (*Table 1*).

Further, an early report by Reck *et al.* on pembrolizumab versus chemotherapy for PD-L1 positive NSCLC patients, also found that HR values for smokers were lower than those of non-smokers (4). It is unlikely that both studies found spurious results. It is possible that PD-1/PD-L1 inhibitors are drugs that may work better in smokers than

**Table 1** HR of smokers and non-smokers of NSCLC patients treated with PD-1 and PD-L1 drugs

Drugs/first author	Drug comparison	Subgroup analysis	Current/#patients	Former/# patients	Never/#patients	Overall/#patients	Note
Pembrolizumab/Mok (3)	Versus chemotherapy	Overall survival in key subgroups	0.71/116	0.60/352	1.10/131	0.69/599	From its appendix
		Tumour proportion Score $\geq 20\%$	0.80/160	0.65/473	1.26/185	0.77/818	
		Tumour proportion Score $\geq 1\%$	0.95/271	0.71/721	1.00/282	0.81/1,274	
Pembrolizumab/Reck (4)	Versus Chemotherapy	Progression-free survival	0.68 /65 (in the intention-to-treat population)	0.47 /216	0.90/24	0.50/305	All are PD-L1 expression on at least 50% of tumor cells
Durvaluma/Sridhar (5)	Study 1108/durvalumab monotherapy	Adjusted HR for OS	Ever vs. never: 0.85 (by Cox proportional hazards model)			–	–
		HR for OS	Ever vs. never: 0.85 (OS by Cox proportional hazards model, including PD-L1/LM subgroups)			–	–
		HR for PFS	Ever vs. never: 0.66 (Cox proportional hazards model, including PD-L1/LM subgroups)			–	–
	ATLANTIC/Durvalumab as third-line or later treatment	Adjusted HR for OS	Ever vs. never: 1.67 (by Cox proportional hazards model)			–	–
		HR for OS	Ever vs. Never: 1.67 (by Cox proportional hazards model, including PD-L1/LM subgroups)			–	–
		HR for PFS	Ever vs. never: 1.08 (by Cox proportional hazards model, including PD-L1/LM subgroups)			–	–

HR, hazard ratio; NSCLC, non-small cell lung cancer; PD-1, programmed death-1; PD-L1, programmed death-ligand 1; LM, liver metastases.

non-smokers while for other drugs non-smokers may respond to treatment better than the smokers.

We examined another publication in which the authors obtained controversial results by analyzing data from two clinical studies (Study 1108 and ATLANTIC) (5) that used a different PD-L1 inhibitor, durvalumab. In Study 1108, the HR values of smoker were lower than those of non-smokers, while the ATLANTIC study found precisely the opposite results. The purpose of Study 1108 was to evaluate the effects of durvalumab monotherapy, whereas the ATLANTIC study evaluated the efficacy of durvalumab as a third-line or later treatment. We reasoned that if the different treatments exerted a differential effect on patients with different treatment histories, this might account for the disparate results between the two studies.

When we compare the reports from Mok *et al.*, Reck *et al.*, Study 1108, and the ATLANTIC study, we see both differences and similarities among the studies (Table 1). The three studies reported by Mok *et al.*, Reck *et al.*, and Study

1108 showed that smokers have better outcomes than non-smokers when PD-1/PD-L1 inhibitors are used as first line *vs.* treatment with single drugs *vs.* others, *vs.* use as a third-line or later treatment in the ATLANTIC study. Our question now is whether smokers will have better outcomes in response to treatment by various individual PD-1/PD-L1 inhibitors than non-smokers.

While lack of data from detailed analyses of smoking status in many cancer treatment trials renders firm conclusions premature at present, extant data suggest that it is worthwhile to explore the effect of smoking history on response to different drug treatments in future studies, especially those of PD-1/PD-L1 drugs. We look forward to seeing more evidence about response to treatment using PD-1/PD-L1 inhibitors from smokers and non-smokers.

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