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# Is smoking history the truly best biomarker for immune checkpoint inhibitor treatment in advanced non-small cell lung cancer?

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Immune checkpoint inhibitors have shown remarkable efficacy in patients with advanced non-small cell lung cancer (NSCLC) and have been approved for these patients. Nivolumab, pembrolizumab and atezolizumab improved outcome of patients with advanced NSCLC compared with docetaxel among patients who had been pretreated with chemotherapy.[1–4] Pembrolizumab improved overall survival among chemo-naive patients with advanced NSCLC and programmed death-ligand 1 (PD-L1) expression in ≥50% of tumour cells.[5] Among patients with PD-L1 levels below 50%, however, pembrolizumab as single agent did not increase progression-free survival or overall survival compared with chemotherapy.[6] Nivolumab failed to improve outcome compared with platinum-based chemotherapy in patients with PD-L1 expression in ≥5%.[7] Among patients with high tumour mutational burden, nivolumab combined with ipilimumab increased overall survival compared with chemotherapy.[8] Combinations of first-line chemotherapy with immune checkpoint inhibitors were recently shown to improve outcome compared with chemotherapy alone.[9 10] Pembrolizumab added to platinum-based chemotherapy increased progression-free survival and overall survival compared with chemotherapy in advanced NSCLC, both among patients with PD-L1 levels ≥1% and those with levels <1%.[9] The addition of atezolizumab to chemotherapy plus bevacizumab also improved outcome including overall survival among patients with metastatic non-squamous cell NSCLC.[10]

While the therapeutic advances with immune checkpoint inhibitors are clinically meaningful, these benefits are limited to a fraction of patients. Within phase III trials, response rates of immune checkpoint inhibitors were higher in the chemo-naive than pretreated patients and highest in combination with first-line chemotherapy.[1–5 9 10] In patients who had been pretreated with chemotherapy, response rates with immune checkpoint inhibitors as single agents were 19%–20% for nivolumab, 29%–30% for pembrolizumab and 14% for atezolizumab, respectively.[1–4] In chemo-naive patients, a response rate of 44.8% was achieved with pembrolizumab among patients with PD-L1 expression in ≥50% of tumour cells.[5] When combined with platinum-based chemotherapy, the response rates were 47.6% for chemotherapy plus pembrolizumab[9] and 63.5% for chemotherapy plus bevacizumab plus atezolizumab.[10]

Because only a fraction of patients benefits from immune checkpoint inhibitors, predictive biomarkers have been of great interest and have been studied as part of the clinical development of immune checkpoint inhibitors. Predictive biomarkers could be based on patient characteristics or tumour features including molecular aberrations. Any clinically useful predictive biomarker should be simple, easy to determine, reliable and cost-effective. A predictive biomarker in patients with advanced NSCLC, however, will most likely never be perfect because of the complexity and heterogeneity of this disease. Despite this limitation, biomarkers can still be clinically useful for selecting or at least enriching patients who will derive the greatest benefit from treatment with immune checkpoint inhibitors.

Smoking-related lung cancer is among those cancers with the highest tumour mutational burden.[11] Smoking-related lung cancers have a higher mutational burden than those of never-smokers. High mutational burden results in the expression of a higher number of neoantigens on the surface of tumour cells which could then serve as targets for the immune system. Consistent with this, immune checkpoint inhibitors were found to be more active in lung cancers of smokers

than in those of never-smokers. Based on a literature review, Norum and Nieder also reported that patients with lung cancer, who were current or former smokers, had higher PD-L1 levels in their tumours and showed a better response to immunotherapy than never-smokers.[12] These findings might suggest smoking history as a biomarker to guide treatment with immune checkpoint inhibitors in patients with advanced NSCLC. In my opinion, however, smoking status is neither the best biomarker nor should it be recommended as a biomarker for guiding treatment with immune checkpoint inhibitors in patients with lung cancer. The reasons for my opinion are several fold.

First, subgroup analyses of data from phase III trials showed inconsistencies with regard to the association between smoking history and benefit from treatment with immune checkpoint inhibitors. The HRs for nivolumab were 1.02 (95% CI 0.64 to 1.61) for never-smokers and 0.70 (95% CI 0.56 to 0.86) for former/current smokers among pretreated patients with non-squamous cell NSCLC[2] whereas the HRs seen with atezolizumab were similar between never-smokers and current smokers among pretreated patients with NSCLC.[4] In chemo-naive patients with PD-L1 levels ≥50%, the benefit of pembrolizumab over platinum-based chemotherapy was seen among former and current smokers but not among never-smokers.[5] The combination of pembrolizumab with first-line chemotherapy benefited both never-smokers and smokers.[9] Therefore, these inconsistencies argue against smoking history for patient selection.

Second, the fact that more than 80% of lung cancers in many countries of the Western world are smoking-related limits the usefulness of smoking history. Considering the degree of smoking, for example, pack-years, might overcome this limitation, although its exact assessment would be challenging in routine practice.

Third, smoking history as selection parameter faces the challenge that never-smokers, who will be aware of the benefits of these drugs, will be inclined to declare themselves as smokers in order to become eligible for treatment with these drugs.

Finally, a predictive biomarker should primarily focus on the therapeutic target of a drug. Immune checkpoint inhibitors in current clinical use are directed against PD-1, PD-L1 or cytotoxic T-lymphocyte associated protein 4. Therefore, expression of these targets on tumour cells and/or immune cells should primarily serve as predictive biomarker(s). The PD-1/PD-L1 system lends itself as a predictive biomarker for anti-PD-1 antibodies or anti-PD-L1 antibodies. Clinical development of these drugs, therefore, focused on PD-L1 expression of tumour cells and/or immune cells. Expression was either part of the inclusion criteria, used for stratification, or assessed in order to determine the association between PD-L1 levels and clinical outcome such as response rate, progression-free survival and overall survival. The clinical studies used different antibodies and different cut-offs. These differences between studies and their potential clinical implications have been critically assessed.[13]

Nivolumab improved outcome compared with docetaxel in patients with squamous cell and non-squamous cell NSCLC. Among patients with squamous cell NSCLC, the survival benefit from nivolumab was slightly higher in those with higher PD-L1 levels.[1] As an example, the HRs were 0.50 (95% CI 0.28 to 0.89) and 0.70 (95% CI 0.48 to 1.01) for PD-L1 ≥10% and PD-L1 <10%, respectively. Among patients with non-squamous cell NSCLC, however, a clear interaction between PD-L1 expression levels on tumour cells and survival benefit achieved with nivolumab was seen.[2] Nivolumab increased overall survival with a HR of 0.40 (95% CI 0.26 to 0.59) among patients with PD-L1 levels ≥10% but did not improve outcome among those with PDL-L1 levels <10% (HR 1.00, 95% CI 0.76 to 1.31). The survival benefit of pembrolizumab over docetaxel was also greater among patients with PD-L1 expression in ≥50% of tumour cells than among those with expression in 1%–49% of tumour cells.[3] The corresponding HRs were 0.53 (95% CI 0.40 to 0.70) and 0.76 (95% CI 0.60 to 0.96), respectively. The atezolizumab trials studied PD-L1 expression on both tumour cells and tumour-infiltrating immune cells as biomarker. The survival benefit of atezolizumab over docetaxel increased with increasing PD-L1 expression.[4] The HRs were 0.41 (95% CI 0.27 to 064), 0.67 (95% CI 0.49 to 0.90) and 0.75 (95% CI 0.59 to 0.96) for TC3 or IC3, TC2/3 or IC2/3, and TC0 and IC0, respectively. Among chemo-naive patients, pembrolizumab improved outcome including overall survival compared with chemotherapy among patients with PD-L1 expression in ≥50% of tumour cells[5] but failed to do so in patients with lower expression.[6] When combined with chemotherapy, the efficacy of pembrolizumab was similar between patients with low and high PD-L1 expression, whereas the efficacy of atezolizumab was more pronounced in patients with high PD-L1 expression.[9 10]

PD-L1 expression levels of tumours (with or without combination of PD-L1 expression on immune cells) can be clinically useful for guiding treatment with immune checkpoint inhibitors in patients with advanced NSCLC. Further translational research should better refine the PD-1/PD-L1 system as predictive biomarker(s). Tumour mutational load lends itself as another predictive biomarker.[8] The current implementation of this biomarker in clinical practice will better define its clinical relevance.

The necessity of predictive biomarkers for immune checkpoint inhibitors might diminish in the future, based on the recent findings. The addition of pembrolizumab to first-line platinum-based chemotherapy improved overall survival among patients with advanced NSCLC, and the magnitude of the survival benefit was clinically meaningful also in patients with PD-L1 expression in <1% of tumour cells in whom the HR was 0.59 (95% CI 0.38 to 0.92).[9] Atezolizumab added to chemotherapy plus bevacizumab improved progression-free survival in both patients with high PD-L1 expression and those with low expression.[10] The HRs for progression were 0.39 (95% CI 0.25 to 0.60) for TC3 or IC3, 0.56 (95% CI 0.41 to 0.77) for TC1/2 or IC1/2 and 0.77 (95% CI 0.61 to 0.99) for TC0 and IC0. In the

future, therefore, it is likely that all patients with advanced NSCLC will be treated with chemotherapy combined with immune checkpoint inhibitors. Whether financial or other considerations will still demand predictive biomarkers for these combinations remains to be seen.

In summary, smoking history should not be used as a predictive biomarker for selecting patients with advanced lung cancer for treatment with immune checkpoint inhibitors. In contrast, research on the PD-1/PD-L1 system as predictive biomarkers should be intensified. Therapeutic advances such as those undoubtedly achieved with immune checkpoint inhibitors, however, must not distract from the worldwide necessity of stricter tobacco control efforts which will eventually result in much greater benefits than any cancer treatment in coming decades will ever be able to achieve.

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