Editorial

# Broader indications for checkpoint inhibitors in NSCLC

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Submitted Jul 29, 2018. Accepted for publication Aug 29, 2018.
doi: 10.21037/jtd.2018.09.06
**View this article at:** http://dx.doi.org/10.21037/jtd.2018.09.06

It has been 23 years since the results from a meta-analysis of several randomized trials comparing first line chemotherapy with best supportive care for metastatic non-small cell lung cancer (NSCLC) was published (1). Although the survival was generally poor, the meta-analysis showed a survival advantage with cisplatin-based chemotherapy, increasing 1-year survival from 5% to 15%. This established palliative chemotherapy as a standard treatment for metastatic NSCLC patients in good performance. Since then modest improvements have been made with pemetrexed maintenance in non-squamous NSCLC and the addition of bevacizumab to the carboplatin-paclitaxel combination (2,3). Trials showing improved progression-free survival (PFS) and quality of life (QOL) with EGFR TKI treatment in NSCLC, and the discovery of specific EGFR mutations as good predictors for this treatment further improved short term outcome for these patients. Subsequently, several other genetic alterations such as ALK/EML, ROS1 and MET have been identified as druggable targets, although only in very small subgroups of patients. Overall, this targeted therapy has led to significant PFS gains but probably not changed the chronicity of the disease and thus long-term survival (4,5).

A breakthrough came with the introduction of immune check point inhibitors (ICPi). These drugs, which are antibodies directed against inhibitory signaling (PD-1/PD-L1) in cytotoxic T cells and cancer cells, have revolutionized the concept of immunotherapy in cancer, in particular malignant melanoma, lung cancer, bladder cancer and lymphoma. As with other cancer treatments, the effect is only seen in some patients (14–23% in unselected patients). Several predictive markers have been suggested with tumor and/or T cell PD-L1 being established as the most used predictive marker although other, such as tumor mutational burden (TMB), alone or in combination, may also find clinical application in the future (6,7). Use of a predictive marker may be more relevant in first line where the chemotherapy alternative show better effect than in later lines. Recently, the KEYNOTE-189 clinical trial showed that pembrolizumab added to standard first-line chemotherapy for patients with metastatic non-squamous NSCLC significantly improved median OS regardless of PD-L1 tumor expression (8). Although OS improvement was seen in all PD-L1 subgroups, the effect was clearly better among patients with tumors that were high PD-L1 expressers. At this time nivolumab, pembrolizumab and atezolizumab have been approved for NSCLC (9).

KEYNOTE-407 similarly was designed to evaluate the addition of pembrolizumab in patients with metastatic NSCLC but of the squamous subtype. A total of 559 patients were randomized to carboplatin + paclitaxel/nab-paclitaxel + placebo or same chemotherapy plus pembrolizumab. After 4 cycles, patients continued with placebo/pembrolizumab until progression or 31 cycles. Cross-over was allowed for patients in the placebo arm. PD-L1 expression in tumor tissue was not a prerequisite for entry; however, patients were stratified prior to randomization based on tumor PD-L1 expression (<1% *vs.* ≥1%) as well as the choice of taxane (paclitaxel *vs.* nab-paclitaxel) and geography (East Asia *vs.* rest of world).

The results reported by at the recent ASCO meeting come from a second interim analysis of the KEYNOTE-407 data after patients had been followed for a median of 7.8 months and enough events occurred to evaluate both OS and PFS (10). Since patients alternatively could have been treated with chemotherapy and ICPi sequentially, the relevant endpoint is OS. The two arms were well balanced. The OS was significantly improved from median 11.3 months in the chemotherapy + placebo arm to 15.9 months in the chemotherapy + pembrolizumab arm (HR =0.64). Subgroup analysis showed no significant differences although a tendency for better HR was seen in females, Asian patients, PS =0

and age ≤65 years. Interestingly, there was no OS difference seen in subgroups defined by PD-L1 expression (HR =0.61, 0.57 and 0.64 for tumor PD-L1 expression of <1%, 1–49% and ≥50% respectively). Conversely, for PFS the usual correlation between outcome and PD-L1 expression was seen (HR =0.68, 0.56 and 0.37 for tumor PD-L1 expression of <1%, 1–49% and ≥50% respectively). Response rates and duration of response also favored the chemotherapy + pembrolizumab arm. Frequency of adverse events were even but a larger proportion of patients discontinued part or all the combination treatment (23.4% *vs.* 11.8%). Immune rated adverse events were off course mainly seen in the pembrolizumab arm.

This study further adds evidence to the combination of ICPi with chemotherapy. The study was well designed and the effect of adding pembrolizumab is impressive with a HR of 0.64. Will this then be the new standard for squamous NSCLC? Previously, the results of the KEYNOTE-189 study of non-squamous NSCLC have led to changes in patient management in some parts of the world. But there are challenges such as cost and added visits for patients which will have a large effect on the uptake of the combination therapy. As always with ICPi trials, one can wonder if a better predictor could make patient selection better and thus further improve the benefit of the ICPi's. TMB is a potential biomarker of response to ICPi's. Using whole-exome sequencing, a higher non-synonymous mutation burden was shown to be associated with significantly improved outcome of ICPi treatment (ORR, PFS, DOR) in NSCLC patients treated with pembrolizumab compared with those with a lower burden (11). Efficacy also correlated with a higher neoantigen burden, and it has been proposed that higher levels of neoantigens formed from nonsynonymous mutations enhance tumor antigenicity and trigger an immune response within the tumor once the inhibition of the PD-1 pathway is prevented by immunotherapy (11).

It will be interesting to understand whether combinations of chemotherapy and ICP is just additive, or whether the chemotherapy enhances the immunologic effect of the ICPi's, because if so, there might be a potential for this treatment to influence survival on a much longer term.

## Acknowledgements

None.

## Footnote

*Conflicts of Interest*: The author has no conflicts of interest to declare.

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**Cite this article as:** Mellemgaard A. Broader indications for checkpoint inhibitors in NSCLC. J Thorac Dis 2018;10(9):5190-5191. doi: 10.21037/jtd.2018.09.06

 