Editorial

# Non-small cell lung cancer: land of conquest for immunotherapy

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*Provenance:* This is an invited Editorial commissioned by the Section Editor Shangwen Dong (Tianjin Medical University General Hospital, Tianjin, China).

*Comment on:* Gandhi L, Rodriguez-Abreu D, Gadgeel S, *et al.* Pembrolizumab plus Chemotherapy in Metastatic Non-Small-Cell Lung Cancer. N Engl J Med 2018;378:2078-92.

Submitted Jul 17, 2018. Accepted for publication Sep 06, 2018.
doi: 10.21037/jtd.2018.09.21
**View this article at:** http://dx.doi.org/10.21037/jtd.2018.09.21

Until recently, one of the main aims of cancer research was finding potential, targetable molecular alterations within neoplastic cells. For lung cancer, this struggle has led to the identification of driver alterations of oncogenes, like *EGFR* mutations and *ALK* translocations. As a result, while chemotherapy regimens have not changed in the last 15 years, the discovery of tyrosine-kinase inhibitors for EGFR (gefitinib, erlotinib, afatinib, osimertinib) and ALK (crizotinib, alectinib, ceritinib, brigatinib) has had an impact on the survival rate of patients with such genetic alterations, although present in less than 15% of non-small cell lung cancer (NSCLC) cases in Caucasian cohorts.

Currently, we are witnessing a paradigm shift from a "tumor-centric" view, to a wider consideration of how cancer-immunity can interplay, which has led to the application of newer, revolutionary immune-based therapeutic approaches.

Among these, immunotherapy using PD1/PD-L1 axis inhibitors has been proven an effective treatment for different tumors and, in particular, NSCLC.

Initially used as a second line therapy for NSCLC, its indication has been subsequently extended as a first line treatment, as monotherapy, for tumors expressing PD-L1 in at least 50% of neoplastic cells (1). More recently, its efficacy has been explored also as neo-adjuvant therapy in resectable NSCLC (2) as well as being in association with chemotherapy as first line treatment in metastatic NSCLC (3). Specifically, in the latter study (KEYNOTE-189), more than 600 therapy naive patients with metastatic non-squamous NSCLC without *EGFR* mutations and *ALK* translocation have been randomized. Of these, 410 have been treated with pembrolizumab and a platinum-based chemotherapy with pemetrexed, while 206 received chemotherapy and a placebo. Response rate, overall survival and progression-free survival, were far higher in the pembrolizumab-combination group. After a median follow-up of 10.5 months, the estimated rate of overall survival at 12 months was 69.2% (95% CI, 64.1% to 73.8%) in the pembrolizumab-combination group versus 49.4% (95% CI, 42.1% to 56.2%) in the placebo-combination group [hazard ratio (HR) for death, 0.49; 95% CI, 0.38 to 0.64; P<0.001]. Median progression-free survival resulted to be 8.8 and 4.9 months in the experimental and control arm, respectively. Importantly, the efficacy of the combination of pembrolizumab plus chemotherapy was observed in all subgroups, including cases with a PD-L1 tumor proportion score (TPS, corresponding to the fraction of tumor cells that express PDL1 on immunohistochemical testing) <1%, although it was more evident in the subgroup with PD-L1 TPS ≥50%. Overall, this study demonstrates that PD1 inhibitors can be combined with chemotherapy with impressive results.

One of the main issues of immunotherapy is the selection of patients who may benefit the most from such treatments, rather than the response to therapy *per se*. Although PD-L1 immunohistochemistry is the only approved test to date for the administration of pembrolizumab, its predictive value appears to be unsatisfactory, to the point that other parameters are being explored (e.g., tumor mutational burden) (4). Taking into account all the possible limitations,

we believe that the predictive potential of PD-L1 immunohistochemistry could be significantly ameliorated by reducing confounding variables, specifically through the harmonization of assays and diagnostic materials (cytology versus diagnostic biopsies versus surgical specimens), in order to overcome existing technical differences between PD-L1 clones and expression heterogeneity within tumors (5,6). In particular, it is necessary to define the minimum number of biopsies for a reliable quantification of PD-L1 for a given tumor, and/or adapt the PD-L1 cutoff to the type of material analyzed. In this regard, the number of cells often reported as the minimum required quantity (100 cells) for PD-L1 determination seems to be too low, given the high degree of PD-L1 expression heterogeneity widely demonstrated in the literature (7).

From the data reported in the KEYNOTE-189 trial by Gandhi and colleagues, it appears that the combination of pembrolizumab-carboplatin-pemetrexed should now be considered as the standard treatment for patients with metastatic non-squamous NSCLC without *EGFR* and *ALK* alterations. It will be necessary to understand whether such results can be replicated also in tumors with squamous histology.

Moreover, as underscored by the authors, one important question remains: how will the strategy of therapy for non-squamous metastatic NSCLC with PD-L1 TPS ≥50% change, should it be pembrolizumab as monotherapy or pembrolizumab plus chemotherapy? We will see. In the meantime, let us celebrate the amazing progress that has been done so quickly against lung cancer thanks to immunotherapy, and to the renewed faith in the extraordinary power of the immune system against cancer.

## Acknowledgements

None.

**Cite this article as:** Munari E, Bogina G. Non-small cell lung cancer: land of conquest for immunotherapy. J Thorac Dis 2018;10(9):5184-5185. doi: 10.21037/jtd.2018.09.21

## Footnote

*Conflicts of Interest:* The authors have no conflicts of interest to declare.

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(English Language Editor: Jeremy Dean Chapnick, AME Publishing Company).

 