Editorial

Immunotherapy supplanting chemotherapy for upfront treatment of advanced non-small cell lung cancer: what's next?

Marius Ilie[1,2,3], Paul Hofman[1,2,3]

[1]Laboratory of Clinical and Experimental Pathology, Pasteur Hospital, FHU OncoAge, University Côte d'Azur, Nice, France; [2]Institute for Research on Cancer and Ageing, Nice (IRCAN), Inserm U1081 and UMR CNRS 7284, University Côte d'Azur, Nice, France; [3]Hospital-Integrated Biobank (BB-0033-00025), Pasteur Hospital University Côte d'Azur, Nice, France

Correspondence to: Paul Hofman. Laboratory of Clinical and Experimental Pathology, Pasteur Hospital, 30 avenue de la Voie Romaine, 06002 Nice, France. Email: hofman.p@chu-nice.fr.

Provenance: This is an invited article commissioned by the Section Editor Tianxiang Chen (Department of Thoracic Surgery, Shanghai Chest Hospital, Shanghai Jiao Tong University, Shanghai, China).

Comment on: Reck M, Rodriguez-Abreu D, Robinson AG, *et al.* Pembrolizumab versus Chemotherapy for PD-L1-Positive Non-Small-Cell Lung Cancer. N Engl J Med 2016;375:1823-33.

Submitted Mar 13, 2017. Accepted for publication Mar 14, 2017.
doi: 10.21037/jtd.2017.03.155
View this article at: http://dx.doi.org/10.21037/jtd.2017.03.155

Pembrolizumab (*Keytruda*, Merck & Co) is the first immunotherapy to be approved by FDA in the USA and by EMA in Europe for first-line treatment of patients with advanced non-small cell lung cancer (NSCLC) and high PD-L1 expression (tumor proportion score of 50% or above). Up to now, a chemotherapy doublet has been the standard of care for these patients, except in patients with advanced NSCLC harboring targetable genomic alterations such as *EGFR* mutations or *ALK* rearrangements.

The approval was based on the results from the phase III KEYNOTE-024 trial, which was presented at the recent European Society for Medical Oncology (ESMO) meeting and simultaneously published by Reck *et al.* (1). The KEYNOTE-024 trial investigated the efficacy of pembrolizumab as first-line comparing to platinum-based chemotherapy in 305 patients with advanced NSCLC demonstrating high level of PD-L1 expression in tumor cells (≥50%).

Pembrolizumab significantly improved the primary endpoint of PFS by approximately 4 months compared to chemotherapy [10.3 *vs.* 6.0 months, hazard ratio (HR) =0.50]. The benefit of pembrolizumab with respect to PFS was positive in all subgroup examined, including patients age (in 141 patients aged <65 years: HR 0.61; in 164 patients aged ≥65 years: HR =0.45). The secondary endpoint of OS was also significantly improved, as per OS at 6 months was 80% vs 72% (HR =0.60) and 1-year OS was 70% *vs.* 54%. Pembrolizumab also showed a higher overall response rate (45% *vs.* 28%) and longer response duration (median, not reached for pembrolizumab *vs* 6.3 months with chemotherapy). The significant improvement in OS with pembrolizumab was remarkable with more than 40% of patient's crossing over from the control arm to pembrolizumab after progression of the disease. Moreover, these data showed notable benefit of pembrolizumab in patients with squamous cell carcinoma of the lung (approximately 20% enrolled in the trial), given the limited treatment options available for these patients for which there is significant biological rationale based on the high mutation burden (2,3). In addition, grade 3, 4, or 5 treatment-related adverse events were half as frequent in the patients treated with pembrolizumab as in those treated with chemotherapy (1).

Based on these results, pembrolizumab is now considered a new standard of care in the first-line treatment of patients with advanced NSCLC and PD-L1 expression of 50% or above.

There are several issues regarding the use of PD-L1 expression as predictive biomarker for immunotherapy (4). While 54% of patients in the KEYNOTE-024 trial were aged ≥65 years, no data on the proportion of PD-L1 expression and response rate to pembrolizumab in

patients over age 70 years are shown. Despite significant advances in the treatment over the past decade, mortality from NSCLC continues to increase in patients over age 70 years (5). It remains difficult to confirm the impact of the immunotherapy in elderly patients, particularly with regard to the decline in the immune function due to immunosenescence, that could, at least in theory, be associated with decreased efficacy of immune mediated therapies (6). Furthermore, the majority of age-unspecified clinical trials include only the fittest of elderly patients due to their stringent eligibility criteria (7). Given the high prevalence of multimorbidity, impairment in physical function and limited social support amongst elderly, the management of this patient group needs to be studied in a more systematic manner (8).

While 30% (500/1,653 patients) of the screened population in this trial showed a strong PD-L1 expression (≥50%), the precise proportion of patients with NSCLC who have a PD-L1 tumor proportion score of 50% or greater needs to be defined, including those with genomic alterations (at least for *EGFR*, *ALK*, *KRAS* alterations) who account for approximately 50% of non-squamous NSCLC. A recent meta-analysis demonstrated that *EGFR* mutation status may be a potential predictive biomarker for OS in advanced NSCLC treated with an immune checkpoint inhibitor *versus* docetaxel (9). No OS advantage in the *EGFR*-mutant subgroup was observed while 34% reduction was noted in the risk for death in the *EGFR* wild-type subgroup (9). In one study of patients with PD-L1 overexpression in more than 50% of tumor cells, patients with *EGFR*-mutant tumors had significantly shorter OS than those with *EGFR* wild-type tumors (median OS=6.5 *vs*. 15.7 months) when treated with pembrolizumab (10). The predictive value of high PD-L1 expression, particularly for the *EGFR*-mutant subgroup, remains unclear to date. Furthermore, the concordance of PD-L1 expression with *EGFR* status, the variation in PD-L1 expression with different types of *EGFR* mutations, and whether the different mutations on *EGFR* have different immunogenicity and hence result in different tumor responses to immune checkpoint inhibition remain unanswered research questions (9).

Several issues related to PD-L1 testing may slow down the immediate benefit performance in clinical practice.

In the KEYNOTE-024 trial, the PD-L1 expression was evaluated on core-needle or excisional biopsy or from tissue resected at the time the metastatic disease was diagnosed, and by using an immunohistochemical assay (PD-L1 IHC 22C3 pharmDx assay, Dako). The positivity was defined by a PD-L1 tumor proportion score of 50% or greater (i.e., membranous PD-L1 expression on at least 50% of tumor cells, regardless of the staining intensity). While in the USA, FDA approved pembrolizumab concurrently with the 22C3 companion diagnostic test for patient selection, in Europe the approval complies with a validated PD-L1 assay. While efforts to harmonize PD-L1 testing across different assays are being conducted Worldwide, this regulatory issue stresses several undefined points for routine clinical practice such as, (I) the concordance between the different existing PD-L1 assays (i.e., CE-IVD, RUO, LDTs), and, (II) whether different cutoff points can identify additional subsets of patients who may benefit from immunotherapy (11-13).

Finally, a minor subset of patients lacking PD-L1 expression may still respond to checkpoint inhibitors, while a relatively significant proportion of patients showing PD-L1 expression may resist *de novo* to the treatment (4). In addition, the high degree of PD-L1 intratumoral heterogeneity may underestimate the PD-L1 status in a biopsy sample compared to the whole tumor burden (14,15). Beyond PD-L1 expression, whether other immune biomarkers can identify additional subsets of patients who may benefit from checkpoint inhibitors is actively under investigation.

Acknowledgements

None.

Footnote

Conflicts of Interest: Paul Hofman is a member of different industrial scientific advisory boards (Roche, AstraZeneca, Novartis, Bristol-Myers Squibb, Pfizer, MSD, Qiagen, Janssen, Biocartis) for which he receives honorarium. Marius Ilié declares no conflict of interest.

References

1. Reck M, Rodriguez-Abreu D, Robinson AG, et al. Pembrolizumab versus Chemotherapy for PD-L1-Positive Non-Small-Cell Lung Cancer. N Engl J Med 2016;375:1823-33.
2. Rizvi NA, Hellmann MD, Snyder A, et al. Cancer immunology. Mutational landscape determines sensitivity to PD-1 blockade in non-small cell lung cancer. Science 2015;348:124-8.

3. Lawrence MS, Stojanov P, Polak P, et al. Mutational heterogeneity in cancer and the search for new cancer-associated genes. Nature 2013;499:214-8.
4. Ilie M, Hofman V, Dietel M, et al. Assessment of the PD-L1 status by immunohistochemistry: challenges and perspectives for therapeutic strategies in lung cancer patients. Virchows Arch 2016;468:511-25.
5. Owonikoko TK, Ragin CC, Belani CP, et al. Lung cancer in elderly patients: an analysis of the surveillance, epidemiology, and end results database. J Clin Oncol 2007;25:5570-7.
6. Suen H, Brown R, Yang S, et al. Multiple myeloma causes clonal T-cell immunosenescence: identification of potential novel targets for promoting tumour immunity and implications for checkpoint blockade. Leukemia 2016;30:1716-24.
7. Shenoy P, Harugeri A. Elderly patients' participation in clinical trials. Perspect Clin Res 2015;6:184-9.
8. Gajra A, Anand A, Loh KP, et al. Treatment dilemma in the care of older adults with advanced lung cancer. J Thorac Dis 2016;8:E1497-E500.
9. Lee CK, Man J, Lord S, Links M, et al. Checkpoint Inhibitors in Metastatic EGFR-Mutated Non-Small Cell Lung Cancer-A Meta-Analysis. J Thorac Oncol 2017;12:403-7.
10. Ramalingam S, Hui R, Gandhi L, et al. P2.39: Long-Term OS for Patients With Advanced NSCLC Enrolled in the KEYNOTE-001 Study of Pembrolizumab: Track: Immunotherapy. J Thorac Oncol 2016;11:S241-S2.
11. Rimm DL, Han G, Taube JM, et al. A Prospective, Multi-institutional, Pathologist-Based Assessment of 4 Immunohistochemistry Assays for PD-L1 Expression in Non-Small Cell Lung Cancer. JAMA Oncol 2017. [Epub ahead of print].
12. Neuman T, London M, Kania-Almog J, et al. A Harmonization Study for the Use of 22C3 PD-L1 Immunohistochemical Staining on Ventana's Platform. J Thorac Oncol 2016;11:1863-8.
13. Ratcliffe MJ, Sharpe A, Midha A, et al. Agreement between Programmed Cell Death Ligand-1 Diagnostic Assays across Multiple Protein Expression Cut-Offs in Non-Small Cell Lung Cancer. Clin Cancer Res 2017. [Epub ahead of print].
14. Ilie M, Long-Mira E, Bence C, et al. Comparative study of the PD-L1 status between surgically resected specimens and matched biopsies of NSCLC patients reveal major discordances: a potential issue for anti-PD-L1 therapeutic strategies. Ann Oncol 2016;27:147-53.
15. McLaughlin J, Han G, Schalper KA, et al. Quantitative Assessment of the Heterogeneity of PD-L1 Expression in Non-Small-Cell Lung Cancer. JAMA Oncol 2016;2:46-54.

Cite this article as: Ilie M, Hofman P. Immunotherapy supplanting chemotherapy for upfront treatment of advanced non-small cell lung cancer: what's next? J Thorac Dis 2017;9(5):E519-E521. doi: 10.21037/jtd.2017.03.155

