



# Is first-line pembrolizumab appropriate for all patients with metastatic non-squamous histology non-small cell lung cancer patients?

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*Provenance:* This is an invited article commissioned by the Section Editor Hengrui Liang (Department of Thoracic Surgery, Guangzhou Medical University, Guangzhou, China).

*Comment on:* Gandhi L, Rodríguez-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 May 07, 2019. Accepted for publication May 20, 2019.

doi: 10.21037/tlcr.2019.05.11

View this article at: <http://dx.doi.org/10.21037/tlcr.2019.05.11>

Immune checkpoint inhibitors have emerged as a new frontier of modern cancer treatment. Prior to recent research in oncogenesis and the immune system, lung cancer treatment was mostly limited to platinum-based chemotherapy, radiation therapy, and surgical resection. Platinum-based chemotherapy has remained the standard of care for stage IV or metastatic non-small cell lung cancer (NSCLC) patients since a landmark meta-analysis in 1995, despite a relatively poor increase in median overall survival (OS) of 1.5 months (1). Incremental progress was seen with the addition of maintenance pemetrexed, but since 2009 the outcomes for patients with metastatic NSCLC without targetable driver mutations had stalled (2).

Research done at the beginning of this decade elucidated the mechanisms some lung tumors use to evade the immune system. Simply put, a cancer cell must exhibit a neoantigen or an overexpression of self-proteins to be recognized as abnormal by the immune system (3). Analysis of lung cancer specimens has shown that NSCLC tumor clonogens can escape the immune system by altering antigen presentation through disruption of the major histocompatibility complexes responsible for accurate detection and destruction by the host immune system (4). Additionally, lung tumors have been shown to inhibit cytotoxic T lymphocyte growth through increased binding of FOXP3+ T regulatory cells to activating cytokines, thus enhancing an immune-suppressing tumor microenvironment (5).

Tumor cells further override the endogenous immune system by inhibiting immune checkpoints. Programmed cell death receptor 1 (PD-1) is a protein primarily expressed by activated B cells, T cells, and NK cells, and regulates T cell activation in surrounding tissue (6). A major breakthrough occurred when it was shown that activation of PD-1 through the programmed cell death 1 ligand (PD-L1) led to immunosuppression through diminished T-cell proliferation and reduced activity (6,7). Knowledge of this pathway spurred intense interest in development of anti-PD-1 and anti-PD-L1 antibodies for augmenting host anti-tumor immunity.

An early phase I study by Topalian *et al.* sought to determine the safety, efficacy and pharmacokinetics of nivolumab, a human IgG4-blocking monoclonal anti-PD-1 antibody (8). Out of the 236 patients with advanced melanoma, NSCLC, prostate cancer or renal-cell/colorectal cancer, 18–28% of patients had an objective response to nivolumab with minimal adverse events. There was a PD-L1 expression-dependent response, since an objective response was observed in 36% of PD-L1-positive tumors and no response was seen for PD-L1-negative tumors (8). These promising results suggested the need to further explore PD-L1 as a cancer biomarker and unveiled the potential benefits of immune checkpoint inhibitors for oncologic treatment.

KEYNOTE-001 was the first clinical trial that explored

the clinical implementation of pembrolizumab, another anti-PD-1 antibody. This trial provided substantial supporting evidence for PD-L1 as a candidate biomarker in predicting response to anti-PD-1 therapies with pembrolizumab in the metastatic NSCLC setting. Garon *et al.* showed that PD-L1 expression on NSCLC tumor cells (verified through immunohistochemistry) correlated to pembrolizumab response rates (9). In the validation cohort, patients with a PD-L1 tumor proportion score (TPS)  $\geq 50\%$  experienced an overall response rate (ORR) of 45.2% and median progression-free survival (PFS) of 6.3 months. However, among patients with TPS  $< 50\%$  the ORR was 10.7–16.5% with a median PFS of approximately 4 months (9). KEYNOTE-001 demonstrated the clinical efficacy of pembrolizumab as an effective antitumor therapeutic and suggested that patients with metastatic NSCLC with TPS  $\geq 50\%$  potentially benefitted the most from this therapy.

The success of KEYNOTE-001 prompted several subsequent trials to determine the role of pembrolizumab in the treatment of patients with metastatic NSCLC. KEYNOTE-024 was an international, multicenter, phase III study that compared upfront pembrolizumab to standard chemotherapy for patients with  $\geq 50\%$  PD-L1 expression (10). It found that within this population of patients with TPS  $\geq 50\%$ , upfront pembrolizumab resulted in significantly longer PFS and OS compared to platinum-based chemotherapy [hazard ratio for death (HR), 0.60; 95% confidence interval (CI), 0.40–0.89;  $P=0.005$ ]. Patients treated with pembrolizumab also had an increased ORR compared to their chemotherapy-treated counterparts, 44.8% (95% CI, 36.8–53.0%) and 27.8% (95% CI, 20.8–35.7%), respectively (10). Therefore, KEYNOTE-024 established upfront use of pembrolizumab and demonstrated its superiority compared to standard chemotherapy for patients with metastatic NSCLC with TPS  $\geq 50\%$  in the first-line setting.

Despite the promising results of KEYNOTE-024 for treatment of patients with PD-L1 expression  $\geq 50\%$ , this cohort represents a minority of patients who present with metastatic NSCLC (9). Given the aggressive natural history of metastatic NSCLC with rapid disease progression, many patients never receive second-line treatment. KEYNOTE-189 was an international, multicenter, phase III trial of standard chemotherapy with or without pembrolizumab in patients with metastatic non-squamous histology NSCLC regardless of PD-L1 TPS (11). Patients were randomly assigned 2:1 to receive either (I) 200 mg of pembrolizumab or (II) saline placebo, in addition to a

platinum-based chemotherapy of the oncologist's choice. Pembrolizumab or the saline placebo were intravenously administered every 3 weeks for up to 35 cycles while simultaneously undergoing four cycles of chemotherapy. All patients had PD-L1 tumor proportion scores assessed by central laboratory review. Throughout the 126 sites in 16 countries, a total of 616 patients were enrolled. The trial demonstrated superior OS in the combination pembrolizumab arm, with an estimated 12-month OS of 69.2% (95% CI, 64.1–73.8%) compared to 49.4% (95% CI, 42.1–56.2%) in the chemotherapy with placebo group (HR for death 0.49, 95% CI, 0.38–0.64,  $P<0.001$ ). The benefit of combination pembrolizumab was seen at all levels of PD-L1 expression. When subdivided by TPS, the greatest benefit was observed in patients with higher PD-L1 expression levels: patients with  $\geq 50\%$ , 1–49%, and  $< 1\%$  tumor proportion scores having HRs for death of 0.42 (95% CI, 0.26–0.68), 0.55 (95% CI, 0.34–0.90) and 0.59 (95% CI, 0.38–0.92), respectively.

Similar advantages in PFS were observed for the combination pembrolizumab group, with a median PFS of 8.8 months (95% CI, 7.6–9.2) in the combination pembrolizumab arm *vs.* 4.9 months (95% CI, 4.7–5.5) for the chemotherapy with placebo group (HR for progression or death 0.52, 95% CI, 0.43–0.64,  $P<0.001$ ). PFS showed a similar PD-L1 TPS-dependent effect, as greater PD-L1 expression levels correlated with longer progression-free survival: patients with  $\geq 50\%$ , 1–49%, and  $< 1\%$  tumor proportion scores having HRs for disease progression or death of 0.36 (95% CI, 0.25–0.52), 0.55 (95% CI, 0.37–0.81) and 0.75 (95% CI, 0.53–1.05), respectively.

Secondary end-points measured included objective response rate to the different combination therapies. As measured by blinded radiological review, the ORR was higher in the pembrolizumab-combination group than in the placebo-combination group across all categories of PD-L1 TPS. The ORR for the pembrolizumab group was 47.6% (95% CI, 42.6–52.5%) *vs.* 18.9% (95% CI, 13.8–25.0%) in the chemotherapy-placebo group ( $P<0.001$ ) (11).

KEYNOTE-189 marks an important milestone in the standardization of anti-PD-1 immunotherapy as first-line treatment for advanced NSCLC allowing greater access to more patients diagnosed with non-squamous histology NSCLC. This study identifies superior outcomes for combined pembrolizumab-chemotherapy in metastatic NSCLC regardless of PD-L1 TPS. This finding is best understood within the context of two similar trials exploring the use of pembrolizumab in advanced NSCLC.

As previously discussed, KEYNOTE-024 established superiority of pembrolizumab monotherapy *vs.* standard chemotherapy for patients with  $\geq 50\%$  PD-L1 expression (10). For patients with rapidly progressive disease, combination pembrolizumab-chemotherapy likely provides added benefit via the rapid anti-tumor activity of platinum-based chemotherapy (12). It remains to be seen whether combination pembrolizumab-chemotherapy is superior to pembrolizumab alone in patients who present with relatively stable disease and high PD-L1 expression, and it is plausible that chemotherapy offers little more than excess toxicity in the first-line treatment of these patients.

The role for combination-pembrolizumab as first-line therapy in patients with  $< 50\%$  PD-L1 expression is potentially confounded by the results of the recent KEYNOTE-042 trial. This international, multicenter, phase III trial randomized patients with locally advanced or metastatic NSCLC with PD-L1 TPS  $> 1\%$  to either pembrolizumab alone or standard chemotherapy (13). It identified a significant improvement in OS for all patients, including those with 1–20% PD-L1 expression (HR 0.81, 95% CI, 0.71–0.93,  $P=0.0018$ ), most of the benefit remain in patients that have TPS  $\geq 50\%$ . This result led to expansion of FDA approval of first-line pembrolizumab for “patients with stage III non-small cell lung cancer (NSCLC) who are not candidates for surgical resection or definitive chemoradiation or metastatic NSCLC” and PD-L1 TPS as low as 1% (14). Although the benefit of pembrolizumab monotherapy for patients with metastatic NSCLC with PD-L1 expression  $\geq 1\%$  is clear based on the results of KEYNOTE-024 and KEYNOTE-042, extreme caution must be exercised regarding patients with unresectable stage III NSCLC who are potentially curable with definitive chemoradiotherapy which remains an important therapy and part of the current standard-of-care in these patients. Pembrolizumab monotherapy has not been evaluated in a phase III trial against this current standard of care for these patients, definitive chemoradiation with consolidation durvalumab (15). Patient candidacy for surgical resection or chemoradiation should always be assessed on an individual basis by multidisciplinary oncological team.

In this context, perhaps the most important finding from KEYNOTE-189 is the demonstrated benefit to inclusion of pembrolizumab for patients with TPS  $< 1\%$ . This represents a paradigm shift in understanding the role of anti-PD-1 and anti-PD-L1 therapy for patients with

zero or minimal upregulation of PD-L1, and it suggests the intriguing possibility that prior or concurrent therapy such as chemotherapy or radiotherapy could boost the host response to immune checkpoint inhibitors. The interplay between immunotherapy and radiotherapy is of particular interest, as ionizing radiation predominantly damages DNA and often results in an immunogenic cell death cascade (16,17). Several preclinical murine models have revealed a synergy between high-dose stereotactic body radiotherapy (SBRT) and immune checkpoint inhibitors, whereby combined therapy is more efficacious than either administered alone (18–20).

Currently, there are a number of clinical trials evaluating the clinical application of combined immunotherapy and radiation treatment. Most ongoing trials are phase I safety and efficacy, but some notable phase II trials include the use of SBRT and anti-CTLA-4 (NCT02221739, New York University) and anti-PD-1 therapy (NCT02658097, Case Comprehensive Cancer Center). A few trials have reported promising early results in abstract form, including PEMBRO-RT which was a randomized phase II study of SBRT and pembrolizumab for metastatic NSCLC regardless of PD-L1 expression (21). This study randomized 74 patients with NSCLC on  $\geq 2$ nd-line therapy and identified a notable extension of PFS to 6.4 *vs.* 1.8 months for the SBRT-pembrolizumab arm *vs.* pembrolizumab alone (HR 0.55, 95% CI, 0.31–0.98,  $P=0.04$ ) (21). In addition, a secondary analysis of patients in the KEYNOTE-001 study identified a cohort of patients treated with pembrolizumab who had also received prior extracranial radiation. Although these patients received prior extracranial irradiation at a median 9.5 months prior to receipt of pembrolizumab, they had significantly longer PFS and overall survival (OS) compared to those who had received pembrolizumab alone and importantly there was no significant difference in grade  $\geq 3$  pulmonary toxicity (22).

The encouraging, yet limited preclinical and clinical data from combining immunotherapy and radiation to target tumor growth reveals the need to further explore the molecular and clinical implication of this dual therapy. While immune checkpoint inhibition as monotherapy demonstrates clear benefit to patients with metastatic NSCLC and PD-L1 expression  $\geq 1\%$ , the potential synergy with radiation should not be ignored as it provides the potential to expand and augment the response across an even larger subset of patients without detectable PD-L1 and help more patients diagnosed with NSCLC.

## Acknowledgments

None.

## Footnote

*Conflicts of Interest:* Dr. Lee has received grant funding for a clinical trial, speaking honorarium, and travel reimbursement from AstraZeneca, Inc. The other authors have no conflicts of interest to declare.

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**Cite this article as:** Le L, van Dams R, Lee P. Is first-line pembrolizumab appropriate for all patients with metastatic non-squamous histology non-small cell lung cancer patients? *Transl Lung Cancer Res* 2019;8(Suppl 4):S327-S330. doi: 10.21037/tlcr.2019.05.11