

# Patient-related outcomes with the use of checkpoint inhibitors for the treatment of metastatic non-small cell lung cancer

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*Comment on:* Brahmer JR, Rodriguez-Abreu D, Robinson AG, *et al.* Health-related quality-of-life results for pembrolizumab versus chemotherapy in advanced, PD-L1-positive NSCLC (KEYNOTE-024): a multicentre, international, randomised, open-label phase 3 trial. *Lancet Oncol* 2017;18:1600-9.

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Lung cancer is the leading cause of cancer mortality worldwide and non-small cell lung cancer (NSCLC) accounts for more than 85% of all lung cancers (1,2). The prognosis for patients with metastatic or stage IV NSCLC is extremely poor with 5-year survival rates of less than 5% (3). Platinum-based chemotherapy is the standard first-line treatment for metastatic NSCLC when genomic testing reveals no activating EGFR mutations, ALK or ROS1 translocation/re-arrangements (found in 10–20% of NSCLC tumors) (4). Platinum-based regimens produce response rates ranging only between 15–30% and are associated with significant toxicities (5,6). However, in the last few years, the opportunity to explore immune therapies for the treatment of metastatic NSCLC has greatly expanded with the identification of the checkpoint inhibitor agents, especially those targeting PD-1/PD-L1 pathway. The PD-1/PD-L1 interaction inhibits T-cell response, induces apoptosis of tumor-specific T cells, and promotes differentiation of CD4 T cells into Tregs and tumor cell resistance (7). Thus, the PD-1/PD-L1 pathway is another crucial self-tolerance pathway that tumor cells hijack to escape immune elimination. In multiple trials, these agents have demonstrated responses in advanced or metastatic NSCLC, with some patients exhibiting durable responses after discontinuing therapy. In 2015, two immune checkpoint inhibitors targeting PD-1, nivolumab and pembrolizumab were approved for second-line therapy of

NSCLC. In 2016, another checkpoint inhibitor targeting PD-L1, atezolizumab was approved for the same indication. These recent approvals position immunotherapeutic agents as the preferred second line therapy for NSCLC. Moreover, the focus of clinical trials is now to investigate the role of these checkpoint inhibitors in the first-line treatment of metastatic NSCLC.

In 2016, results were reported from the phase III, KEYNOTE-024 trial that tested pembrolizumab, a high affinity humanized IgG4 antibody targeting PD-1 as first line therapy for metastatic treatment-naïve NSCLC compared to chemotherapy (8). In this trial, 154 patients with previously untreated advanced NSCLC with PD-L1 expression on at least 50% of tumor cells and no sensitizing EGFR mutation or ALK rearrangement received pembrolizumab and 151 received the investigator's choice of platinum-based chemotherapy. Crossover from the chemotherapy group to the pembrolizumab group was permitted in the event of disease progression. The primary end point, progression-free survival (PFS) was significantly longer in the pembrolizumab group compared to chemotherapy group (10.3 *vs.* 6.0 months; HR 0.50;  $P < 0.001$ ). The overall survival (OS) was also significantly better in the pembrolizumab group *vs.* the chemotherapy group (HR 0.60; 95% CI, 0.41–0.89;  $P = 0.005$ ). The response rate was 44.8% in the pembrolizumab group and 27.8% in the chemotherapy group. Based on the

significant improvement in PFS and OS reported by this study, FDA approved pembrolizumab for the first-line treatment of patients with metastatic NSCLC whose tumors express PD-L1 on at least 50% of tumor cells. Of note, the toxicity profile was much more favorable for pembrolizumab as compared to chemotherapy. Treatment-related adverse events (AEs) of any grade occurred in 73% of the patients in the pembrolizumab group compared to 90% in the chemotherapy group. Similarly, severe AEs (grade 3 or higher) occurred in only 27% of the patients in the pembrolizumab group compared to 53% in the chemotherapy group. The most common serious AEs were diarrhea (in 3.9% of the patients) and pneumonitis (2.6%) in the pembrolizumab group and, anemia (19.3%), neutropenia (13.3%), thrombocytopenia (5.3%) and neutropenia (4.0%) in the chemotherapy group.

In 2017, Brahmer and colleagues reported exploratory results from KEYNOTE-024 described above in *The Lancet Oncology* comparing patient-reported outcomes including quality of life between the pembrolizumab and chemotherapy groups (9). Patient reported outcomes (PRO) were assessed at day 1 of the first three cycles followed by every 9 weeks thereafter using the European Organization for the Research and Treatment of Cancer (EORTC) questionnaires. Compliance with the PRO questionnaires was greater than 90% at baseline and approximately 80% at week 15 for both groups. At 15 weeks, global QOL score for pembrolizumab was significantly improved compared to chemotherapy with a between-group difference of least-squares mean scores of 7.8 (95% CI: 2.9–12.8; two-sided nominal  $P=0.0020$ ). Time to deterioration of tumor symptoms (a composite of cough, dyspnea, and chest pain) was improved with pembrolizumab than with chemotherapy (median not reached *vs.* 5.0 months; hazard ratio 0.66,  $P=0.029$ ). Also, pembrolizumab was associated with greater improvement in QOL than was chemotherapy among patients without disease progression, and with less worsening in QOL among those with disease progression. These findings suggest that pembrolizumab improves or maintains QOL regardless of disease status. Overall, pembrolizumab was associated with a clinically meaningful improvement in QOL compared with that for chemotherapy as first-line treatment in patients with metastatic NSCLC.

In the past decade, patient-focused care is becoming a critical component of quality health care. A large single-center randomized trial reported that integration of PROs in routine clinical oncology care improves

outcomes such as QOL, emergency room utilization and survival in patients (10). Use of PROs as an outcome measure in clinical trials is becoming more common with more than 27% of trials registered from November 2007 to December 2013 using them (11). However, one main issue is that often trials do not report results for the PRO or QOL measures even though this data is collected as part of the trial. A retrospective review of clinical trial protocols approved by six research ethics committees in Europe between 2000 and 2003 reported that of the 173 cancer trials, 90 (52%) specified QOL outcomes in their protocol but only 35 (20%) reported QOL outcomes in a corresponding publication (12). The availability of QOL results along with the primary results allows a timely evaluation of the benefit-to-risk ratio and of the value of the treatment. However, measurement of QOL outcomes can be time-consuming, expensive and increase trial complexity. Therefore, the investigators of KEYNOTE-024 should be appreciated for collecting as well as reporting the QOL findings within a year of reporting the primary outcome results. Also, in this study, more than 90% of the patients participated in completing the questionnaires. Therefore, this study does report strong evidence in support of improved PROs with immunotherapy as compared to chemotherapy. This finding provides an additional reason to support the use of immunotherapy in first-line setting for metastatic NSCLC in tumors with PD-L1 expression  $\geq 50\%$  of tumor cells. One limitation of the study was that the instruments and questionnaires used for measurement of the QOL measured were not developed for use with immunotherapy. However, they do collect information about the major symptoms that patients with lung cancer experience. The National Cancer Institute's Patient-Reported Outcomes version of the Common Terminology Criteria for Adverse Events (PRO-CTCAE) is being evaluated by multiple stakeholders, including the FDA, and is considered a promising tool to provide a method to assess symptomatic AEs from the patient perspective in clinical trials (13).

A similar improvement in QOL has also been reported by a few other studies with checkpoint inhibitors. KEYNOTE-010 compared the efficacy of pembrolizumab with chemotherapy (docetaxel) in patients with metastatic NSCLC with PD-L1 expression  $\geq 50\%$  in tumor cells who have progressed on prior platinum-based chemotherapy. This study reported an improvement in global QOL by 8.3 points with pembrolizumab (two-sided nominal  $P=0.006$ ) (14). CheckMate 067 compared the efficacy of

nivolumab, a monoclonal antibody of PD-1, combined with ipilimumab, as combination therapy on one hand and nivolumab as monotherapy on the other in patients with metastatic melanoma. Both groups reported no clinically meaningful deterioration in QOL over time including in patients who discontinued treatment for any cause (15). One possible explanation for the improvement in QOL with immunotherapy agents such as pembrolizumab when compared to chemotherapy could be the favorable toxicity profile with these agents. A meta-analysis of 25 trials with 10,794 patients across five different cancers compared therapy with checkpoint inhibitors to chemotherapy (16). Treatment-related deaths were reported for only 0.6% of the patients. Treatment discontinuations were less frequent for PD-1 or PD-L1 inhibitors than chemotherapy (5.8% *vs.* 13.3%,  $P < 0.001$ ). PD-1/PD-L1 inhibitors also had less grade 3, 4, and 5 AEs than chemotherapy (13.8% *vs.* 39.8%,  $P < 0.001$ ). There were also significantly lower risks of experiencing serious AEs with PD-1/PD-L1 inhibitor over chemotherapy in the lung cancer than melanoma trials (RR lung 0.33 *vs.* RR melanoma 0.46,  $P$  for interaction = 0.01). This could be likely due to more treatment-related AEs experiences with standard chemotherapy regimens used in lung cancer treatment. Of note, although anti-PD-1 and anti-PD-L1 antibodies show significant clinical benefits, they can lead to immune-related adverse events (irAEs) by increasing immune system function. These autoimmune side effects are significantly less frequent than the toxicities observed with chemotherapy but can be quite severe requiring management with anti-inflammatory drugs such as steroids or infliximab. Significant patient education and vigilant oversight are needed to address these auto immune-related toxicities quickly to avoid development of severe symptoms.

In conclusion, the results from Brahmer and colleagues show a clear benefit in health-related QOL, supporting the use of pembrolizumab as first-line treatment in advanced NSCLC with expression of PD-L1 on at least 50% of tumor cells. The significant improvement in QOL is expected given the improved efficacy and favorable toxicity profile of pembrolizumab compared to chemotherapy. Moreover, these results are also applicable to the use of immunotherapy in other clinical settings and provide important insight into the patient-reported outcomes and QOL of patients on these agents. Health-related QOL measurement in clinical trials greatly aids clinical decision making and should be encouraged in all planned trials.

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## Footnote

*Conflicts of Interest:* Jyoti Malhotra has served on the advisory board for Pfizer and Astra-Zeneca. Salma K. Jabbour receives research funding from Merck and Nestle.

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