Editorial Commentary

Are we facing a cure in lung cancer?—KEYNOTE-001 insights

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Pembrolizumab is a humanized monoclonal antibody that blocks the programmed death 1 receptor (PD-1) and has antitumor activity in advanced non-small-cell lung cancer (NSCLC). The phase 1 trial first published in 2015, included a total of 495 advanced NSCLC patients. The patients received pembrolizumab at a dose of either 2 or 10 mg per kilogram of body weight every 3 weeks or 10 mg per kilogram every 2 weeks with progression-free survival (PFS) of 3.7 months and median duration of response (DOR) of 12.5 months. Among all patients, the median overall survival (OS) was 12.0 months. In patients with a PD-L1 immunohistochemistry [tumor proportion score (TPS)] score of at least 50% the median PFS was 6.3 months and the response rate was 45.2%, thus, the median OS was not reached (1).

In short, this is the first data that gives hope and shows improvement in OS, for patients with advance NSCLC with PDL1 expression at minimum of 50%.

The outstanding results of KEYNOTE-001 led to a revolution in the field of lung cancer treatment, leading to the incorporation of pembrolizumab as the backbone of therapy in NSCLC therapy either as first- or second-line therapy.

In the years that followed numerous trials of pembrolizumab in the first line-setting showed improved OS versus platinum-based chemotherapy in patients with advanced NSCLC without epidermal growth factor receptor (EGFR) and anaplastic lymphoma kinase (ALK) alterations and PD-L1 TPS of 50% or greater (KEYNOTE-024) (2) and PD-L1 TPS of 1% or greater (KEYNOTE-042) (3).

Currently, the standard-of-care in first-line therapy is pembrolizumab in combination with platinum doublet chemotherapy, based on confirmatory phase 3 trials, KEYNOTE-189 (non-squamous) (4) and KEYNOTE-407 (squamous) (5). Similar results have also been seen in trials with other immune checkpoint inhibitors (ICI) (6-8).

An updated analysis of KEYNOTE-001 reported by Shaverdian *et al.* in 2017, showed longer median PFS (6.3 versus 2 months) and median OS (11.6 versus 5.3 months) in patients who previously received any radiotherapy than in patients without previous radiotherapy, respectively (9), probably because of the abscopal effect due to massive cell death and released neoantigen post radiotherapy, which promote priming of immune cells against tumor antigens (10).

A recently published meta-analysis by Zhou *et al.* of five KEYNOTE trials evaluated indirectly the efficacy of pembrolizumab monotherapy versus pembrolizumab plus chemotherapy in the first-line therapy of patients with advanced NSCLC and PD-L1, TPS ≥50%. The study concluded that combination therapy further improves the outcomes (11).

A new analysis of KEYNOTE-001 recently published by Garon *et al.* in 2019, reports the longest follow-up of efficacy and safety with median follow-up of 5 years for

both treatment naïve and previously treated patients with advance NSCLC with PD-L1 positivity, and TPS of at least 50% treated with pembrolizumab monotherapy. The study showed that the estimated 5-year OS was 29.6% for treatment-naive patients and 25.0% for previously treated patients, with no late-onset grade 4 or 5 treatment-related adverse events. The previously (pre-immunotherapy era) reported 5 years survival in this population is about 5.5% (12). Now, with 5-year OS close to 30%, the possibility of cure in some patients for advanced NSCLC is real.

Interestingly, of the 74 patients with an EGFR mutation included in the group of previously treated patients that received pembrolizumab monotherapy, 9 patients from this group were still alive after a median of 5 years, (PD-L1 status not documented). The results presented lead us to the question of the role of immunotherapy in patients with EGFR/ALK driver mutations. Is combination immunotherapy with a tyrosine kinase inhibitor (TKI) superior to TKI monotherapy? Because the study presents only the OS of this group it is not known whether the improved survival is due to further lines of TKIs or to pembrolizumab.

It is important to note that Lisberg *et al.* showed that in EGFR mutated patients with PD-L1 TPS of at least 1% or even ≥50% there was no advantage to adding pembrolizumab to TKI naïve patients with advanced NSCLC (13). In a phase Ib trial reported by Ahn *et al.* the combination of EGFR-TKIs with durvalumab showed no benefit and was associated with a high rate of pneumonitis (14). Interestingly, in a study by Rudin *et al.* an increase in PD-L1 expression and CD8+ T-cell tumor infiltration were seen in some patients after EGFR-TKI therapy (15).

Despite the outstanding survival rates, there are still patients who do not respond to pembrolizumab or do respond but develop acquired resistance. In KEYNOTE-001 five patients progressed after 3 years on pembrolizumab most probably due to development of acquired resistance. Four patients received pembrolizumab beyond progression for 2 to 3.5 years. The efficacy of immunotherapy, is currently limited due to mechanisms of resistance. The results so far of clinical trials have led us to the beginning of an understanding of the mechanisms of resistance to immunotherapy. By further analyzing those mechanisms and establishing new strategies to counter them, the efficacy of immunotherapy could be significantly improved (16).

In summary, the 5-year follow-up of the KEYNOTE-001 trial shows a long-term OS benefit with a manageable safety profile for PD-L1-expressing treatment-naive advanced NSCLC. Better efficacy was observed in patients with TPS ≥50% with estimated 5-year OS of 29.6% for treatment-naive patients and 25.0% for previously treated patients. We are entering a new era where metastatic lung cancer is potentially curable, at least in terms of 5-year OS.

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Footnote

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

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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