



Pembrolizumab—the “KEY” to an evolving landscape in treatment of squamous non-small cell lung cancer (NSCLC)

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Squamous cell histology constitutes about 25–30% of all non-small cell lung cancers (NSCLC) (1), and because of the lack of targetable mutations, remains a challenge to treat. For many years, cytotoxic chemotherapy doublet, which includes a platinum agent (carboplatin or cisplatin), has been the standard of care for metastatic squamous NSCLC. Over the last 1–2 years, with an improved knowledge regarding the biology of tumor and evolution in the role of Immunotherapy, treatment algorithms in NSCLC are evolving at a rapid pace. Identifying patients and disease types which are most likely to benefit from immunotherapy has become an increasingly important area of research. Cytotoxic chemotherapy has been replaced by pembrolizumab in the first-line setting as the preferred choice of treatment for patients with metastatic NSCLC whose tumors have a programmed death ligand 1 (PD-L1) tumor proportion score (TPS) greater than 50%, regardless of histology (2).

The results of KEYNOTE-407 came at a time where the treatment of NSCLC is becoming increasing complex. In this study, Dr. Paz-Ares and colleagues studied whether adding pembrolizumab to standard chemotherapy improved outcomes in individuals with previously untreated metastatic squamous NSCLC. In this phase III, placebo-controlled, double blind trial, 559 patients from 17 countries with treatment-naive metastatic squamous cell

NSCLC (stage IV) were randomized in an equal proportion to receive pembrolizumab plus carboplatin and either paclitaxel (60.1% patients) or nanoparticle albumin-bound (nab)-paclitaxel for 4 cycles *vs.* the same chemotherapy plus placebo (3). The experimental arm received further pembrolizumab for up to 31 cycles, whereas the control arm received placebo. Randomization was stratified according to PD-L1 expression on tumor cells [$\geq 1\%$ (63% of patients) *vs.* $< 1\%$], the taxane used and geographic regions [East Asia (19% of patients) *vs.* the rest of the world] (3). The treatment assigned was then continued until disease progression confirmed through radiologic assessments, intolerable toxicities, patient consent withdrawal or by investigator's choice. If a patient had radiographically confirmed progression while on placebo, they are allowed to cross over to the Pembrolizumab arm (31.7% patients in the placebo group crossed over) (3).

After a 7.8-month median follow-up interval, the median overall survival in the pembrolizumab-containing arm was significantly improved with 15.9 months [95% confidence interval (CI): 13.2 months to not reached] *vs.* 11.3 months (95% CI: 9.5–14.8 months) in the chemotherapy arm ($P=0.0008$). Pembrolizumab arm revealed a superior overall survival among all predefined subgroups. Notably, across all the PD-L1 TPS subgroups, the extent of survival benefit with pembrolizumab added to chemotherapy was similar.

The reported survival rates at one year in individuals with PD-L1 score of <1% were 64.2% in the pembrolizumab group as compared to 43.3% in the placebo group. The corresponding numbers were 65.9% and 50.0% in the TPS 1–49% cohort and 63.4% and 51.0% in the TPS \geq 50% cohort. Progression-free survival also favored the pembrolizumab/chemotherapy arm: median of 6.4 *vs.* 4.8 months ($P < 0.0001$). Similar to overall survival data, progression-free survival across all the three PD-L1 TPS subgroups was also noted to be better with the addition of pembrolizumab. However, the reduction in the disease progression rate was proportional to the percentage expression of PD-L1 in tumor. The objective response rate was remarkably higher in the pembrolizumab plus chemotherapy arm: 57.9% *vs.* 38.4%, respectively ($P = 0.0004$) (3).

The relative number and severity of adverse events between the two groups were similar, with about 98% of patients reporting an adverse event and 69% experiencing grades 3 to 5 adverse events. Adverse events of grade 3 or higher were reported in 68.2% of the placebo/chemotherapy group and in 69.8% of the pembrolizumab/chemotherapy group (3). Adverse events that lead to treatment discontinuation were more frequent in the pembrolizumab arm (13.3% *vs.* 6.4%). Adverse events led to death in 8.3% *vs.* 6.4% of patients, with death considered to be potentially related to treatment in 3.6% *vs.* 2.1%. Adverse events that are immune-related and of any grade were more frequent in the pembrolizumab arm, 28.8% (10.8% grade \geq 3) *vs.* 8.6% (3.2% grade \geq 3) (3). However, these were not unexpected with the most common ones being hypothyroidism, hyperthyroidism and pneumonitis.

The results of this study revealed that the addition of pembrolizumab to standard chemotherapy, in comparison to chemotherapy doublet alone, increased median progression-free survival by 1.6 months (6.4 *vs.* 4.8 months) and median overall survival by a of 4.6 months (15.9 *vs.* 11.3 months), with similar incidence of treatment associated adverse effects (3).

The goals of management for patients with advanced NSCLC recognizing palliative intent of treatment are to prolong survival and to maintain quality of life for as long as possible, while minimizing the side-effects as a result of treatment. Recent advances in lung cancer treatment are evolving from novel therapies that are developed to target inhibitory T-cell receptors, like programmed cell death ligand 1 (PD-L1) or programmed cell death-1 (PD-1) and cytotoxic lymphocyte-associated antigen-4 (CTLA-4) (4).

The results of the KEYNOTE-407 study build upon previous immunotherapy trials in NSCLC. Nivolumab, was first reported to improve overall survival in the second line setting as compared to docetaxel in advanced NSCLC (5,6). Similarly, the KEYNOTE-010 showed an overall survival advantage for pembrolizumab over docetaxel for previously treated, PD-L1 positive (\geq 1%) advanced NSCLC (7). Pembrolizumab was then approved for metastatic NSCLC as a first line therapy in patients with PD-L1 score \geq 50% as it revealed a remarkably prolonged overall survival and progression-free survival as compared to chemotherapy and with fewer adverse events in KEYNOTE-024 trial (2). In KEYNOTE-189 study, overall survival was prolonged in untreated non-squamous, metastatic NSCLC without EGFR or ALK alterations by adding Pembrolizumab to Platinum-Pemetrexed chemotherapy doublet (8).

The KEYNOTE-407 data for untreated metastatic squamous cell lung cancer show benefit across all subtypes of patients with squamous cell carcinoma, irrespective of expression of PD-L1. PD-L1 TPS has been recognized as a trust-worthy biomarker to select individuals with advanced NSCLC for treatment with single agent Pembrolizumab in the first line setting on the basis that there is a well-recognized relationship indicating that the magnitude of benefit from Pembrolizumab is proportional to the degree of PD-L1 expression among tumors (9). This study negated the impression that upfront combination immunotherapy-chemotherapy is probably not beneficial in metastatic squamous NSCLC.

Despite the results, this study has certain key limitations. This study included only patients with ECOG 0/1, while a considerable proportion of patients we see in our day-to-day practice include patients with a functional status of ECOG 2 or worse. Can these results be extended to this population as well or would there be an increase in the incidence of immune related adverse events in this subgroup? One other limitation of this study would be exclusion of a subgroup of patients with symptomatic brain metastases. Approximately, 20% of patients with NSCLC present with brain metastases and approximately 50% of the patients will develop brain metastases during the course of the disease (10). With the recognition and development of driver mutations in non-squamous NSCLC, targeted therapies with EGFR/ALK/ROS inhibitors have provided durable responses in patients but surgical resection, stereotactic radiosurgery (SRS) and whole brain radiation therapy (WBRT) have been the primary treatment modalities in squamous NSCLC. This study included only 20 patients with asymptomatic brain

metastases in pembrolizumab/chemotherapy arm and 24 patients in the chemotherapy/placebo arm and hence limited any evidence-based conclusion, and would warrant more investigation in this area of research.

One other consideration is that although trials have demonstrated that tumor PD-L1 expression is associated with increased likelihood of response to checkpoint inhibitors, it neither guarantees response in those with high tumor PD-L1 expression nor eliminates the possibility of response in those tumors that lack PD-L1 expression. There may be PD-L1 heterogeneity within tumors and between tumor sites and tumor PD-L1 expression can change over time in response to therapy. Although the protocol design specifies that patients from placebo-group can crossover to the single-agent checkpoint inhibitor group after progression or therapy discontinuation, only about 31.7% and 42.8% in the intention-to-treat population and among those patients who discontinued therapy, respectively, crossed over which is relatively low (11). Therefore, there is unclear evidence as to whether combination chemo-immunotherapy in the first-line setting is more beneficial than the sequential strategy in patients with squamous NSCLC. One other drawback would be shorter follow up (median 7.8 months). Most patients tolerate therapy well, however, immune-related adverse effects can happen at any point of time while on treatment. With improved overall survival, it is not uncommon to see adverse events from immunotherapy long after it was started. Long-term safety and efficacy data are currently lacking in a large randomized control trial population to our knowledge, hence it becomes especially important to assess long-term side effects that may develop as a consequence of widespread utilization of Immunotherapy.

In regards to overall quality of life, a recently published study reported patient reported outcomes (PROs) in KEYNOTE-407 in the form of health-related quality of life (HRQoL) questionnaires at baseline, week 9 and week 18 (which is during and after treatment with platinum agents) (12). Quality of life was improved or maintained in pembrolizumab-chemotherapy combination group rather than chemotherapy group alone at all stages of assessment further reiterating the safety of adding Pembrolizumab. With improvement in cancer survivorship, emphasis on quality of life becomes all the more important.

To conclude, KEYNOTE-407 by Dr. Paz-Ares *et al.* has paved the role for upfront use of pembrolizumab in combination with chemotherapy for untreated metastatic squamous NSCLC with improvement in progression-

free survival and overall survival across all PD-L1 subtypes offering hope to numerous patients that are affected by this arduous disease. This is now the new standard of care for these patients. However, ongoing follow up of this trial is important to recognize the long-term side effect profile and efficacy.

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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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