An extended overall survival analysis of pemetrexed and carboplatin with or without pembrolizumab as first-line therapy for advanced non-squamous non-small cell lung cancer

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Some non-small cell lung cancer (NSCLC) have "Driver" genomic abnormalities, such as epidermal growth factor receptors (EGFR), anaplastic lymphoma kinase (ALK) abnormal fusion, mesenchymal-epithelial transition (MET) amplification etc. There are various targeted agents developed directed against these mutations, with significant improvement in outcomes (1,2). However, in the majority of NSCLC patients without any molecular targets, a doublet platinum-based therapy has been used as first-line therapy in combination with different agents such as pemetrexed (a folate metabolite) (3).

Monoclonal antibodies (mAbs) against immune checkpoints such as programmed death cell protein (PD)-1 (pembrolizumab, nivolumab) and programmed death cell-ligand (PD-L)-1 (atezolizumab, durvalumab) have been developed and approved by US Food and Drug Administration (FDA) in NSCLC (4-7). Nivolumab showed improved overall survival (OS) compared to docetaxel in NSCLC patients who have already been progressed on platinum doublet therapy (9.2 *vs.* 6 months, HR 0.59, P≤0.001) (8). KEYNOTE-024 phase III clinical trial compared pembrolizumab to the investigator's choice cytotoxic chemotherapy in treatment-naive NSCLC patients with PD-L1 score of >50%. Patients who received pembrolizumab were found to have improved objective response rate (ORR) and progression-free survival (PFS) compared to the chemotherapy [(44.8% *vs.* 27.8%) and (10.3 *vs.* 6.0 months, HR =0.50, P<0.001) respectively] (7). Atezolizumab have also shown significantly improved OS in NSCLC patients compared to docetaxel after progression on platinum-based therapy (6). Recently, the FDA has also expanded the use of durvalumab (an anti-PD-L1) in unresectable stage III NSCLC patients after completion of concurrent chemoradiation (9). This approval was based on the results of PACIFIC trial (10).

Although these immune checkpoint inhibitors (ICI) have shown better efficacy and manageable toxicities in NSCLC compared to the standard chemotherapy, long-term follow-up of such patients on clinical trials has shown an evidence of delayed progression, thought to be due to an emergence of acquired and innate resistance in various solid tumors including lung cancer (11-13). Impaired formation of T-cell memory, insufficient generation of anti-tumor T cells and inadequate function of tumor specific T cells have been the cause of treatment failure and emergence of resistance after long-term therapy with ICI (12,13). Such observations have encouraged clinicians and scientists to look at other therapeutic modalities including a combination therapies in lung cancer. Exciting developments have been made in NSCLC patients using ICI in combination with chemotherapies such as platinum-based doublet therapy. Pre-clinical models and clinical

studies have demonstrated that the chemotherapeutic agents not only have cytotoxic effects, they can further enhance the host immunity against the tumor cells via various mechanisms (14). The chemotherapeutic agents enhance the PD-L1 expression on the tumor cells that can be the target of mAbs against the PD-L1 expressing tumor cells (15,16). These observations have led to the exploration of the synergistic effects of chemotherapy with immunotherapy such as pembrolizumab. Pembrolizumab was combined with carboplatin/pemetrexed in a phase-1 clinical trial and showed significantly higher response rate and increased PFS (17). Subsequently, in cohort G of the phase 2 KEYNOTE-021 clinical study (an open labelled randomized phase 2 clinical trial) the combination of pembrolizumab with carboplatin/pemetrexed (PC) showed significantly improved PFS and response rate (18).

In this brief report, published in *Journal of Thoracic Oncology*, Borghaei *et al.* provide an updated analysis (24 months survival analysis) of Cohort G of KEYNOTE-021. Borghaei *et al.* report that the significantly improved PFS and ORR in NSCLC patients who have received pembrolizumab plus PC compared to PC alone was also maintained 24 months following the original analysis (19). This updated analysis is commendable and is of great significance in real word as it provides the long-term outlook of the patients in clinical trial. The results of this phase 2 trial lead to an expedited approval of pembrolizumab + PC combination by the FDA in 2017 (20). The original phase 2 trial included 123 patients with previously untreated stage IIIB/IV non-squamous NSCLC without EGFR and/or ALK receptor tyrosine kinase gene aberrations. The median follow-up was 10.6 months, the ORR [(55% *vs.* 29%, P=0.0016) and PFS (HR =0.53, 95% CI: 0.31–0.91, P=0.010) were significantly better in pembrolizumab + PC cohort compared to PC alone. Although grade 3 or worse treatment-related adverse events were slightly higher in pembrolizumab + PC cohort (39% *vs.* 26%), the risk-benefit ratio favored the use of pembrolizumab + PC compared to PC alone (18). These findings from this trial were validated in a larger phase III study (KEYNOTE-189) (21).

In this updated analysis, the authors have pursued the well-designed original study longitudinally and have achieved the median follow-up of approximately 24 months compared to 10.6 months in original study. Patients in PC only cohort were allowed to cross-over to pembrolizumab + PC cohort to allow beneficence across the study population. The primary and secondary endpoints were maintained (PFS, ORR, and OS) as well in this analysis. This analysis demonstrates that the patients in the pembrolizumab + PC arm maintained the same efficacy and safety profile as in the original study. In this article, the authors have further compared these results with the phase 3 clinical trial (KEYNOTE-189) and have shown similar results (21). We agree with the authors that, despite issues with cross trial comparison, the similarities between this updated analysis and those of KEYNOTE-189 and KEYNOTE-024 (22) are noteworthy. Although, the patients with expected poor outcomes (e.g., untreated brain metastasis) have been excluded from the original study, and the impact of this exclusion can be seen in the form of extended median OS in PC only cohort compared to the historical response rate to PC only therapy (23), and that the combination arm not being able to achieve median OS even after 23.9 months of median follow-up, the results of this analysis can lay basis for future trials on patients with aggressive disease such as with brain metastasis as well as in patients who have progressed previously on first line therapy. In the KEYNOTE-021 follow up report, 26 (46.6%) patients on the PC only arms were allowed a crossover to pembrolizumab + PC following discontinuation (due to progression) or completion of the PC treatment, however a detailed analysis on these patients is not available. Although, we do know that of the 35 patients who passed away, 26 (74%) patients had received second line immunotherapy (19), the detailed outcome analysis on such patients would have been helpful to ascertain the utility of pembrolizumab + PC combination as a second line therapy after progression on first line chemotherapy. Pembrolizumab, as a monotherapy has been used in NSCLC patients with brain metastasis and have shown significantly improved results (24), however there is a need to study the chemotherapy and immunotherapy combination in such patients. After FDA approval of pembrolizumab + PC, we started using this combination at our institute in NSCLC patients with brain metastasis. ORR was higher in patients with brain metastasis receiving pembrolizumab + PC (80% *vs.* 58.3%) (25). A 30 months follow-up of this study population showed median PFS of 5.9 months in patients receiving PC + pembrolizumab. Of the patients, who had brain metastasis, the median PFS was 6.5 months. ORR remained the same and none of the additional patients from our cohort (PC + pembrolizumab) achieved complete remission (CR). Median OS is 15.0 months in overall cohort and 13.7 months in subset of the patients with brain metastasis.

The authors further report that the safety profile of the pembrolizumab + PC combination was also maintained in this updated analysis. Although, pembrolizumab + PC combination will result in higher proportion of patients experiencing grade 3 or 4 adverse events, there is no evidence that PC potentiate the toxicity of the pembrolizumab except in case of renal toxicity (21).

In conclusion, chemotherapy in combination with immunotherapy have shown promising results in pre-clinical, clinical phase 1, 2 and 3 trials. Long-term analysis of the KEYNOTE-021 trial have maintained the original efficacy and safety profile. Despite a relatively higher rate of adverse events in pembrolizumab + PC cohorts when compared to PC alone (41% *vs.* 27%), the risk benefit ratio favors the use of this combination due to significantly improved treatment related outcomes with pembrolizumab + PC use. Although, KEYNOTE-189 clinical trial included the patients with brain metastasis, contrary to the KEYNOTE-021, the detailed outcome analysis such as ORR, OS, PFS was still missing. However, less proportion of patients with brain metastasis progressed in pembrolizumab + PC cohort (21). Another phase II clinical trial on NSCLC is recruiting patients using the combination of avelumab with chemotherapy, however this trial is also excluding the patients with the brain metastasis (NCT03568097). We believe future studies are needed with detailed outcome analysis in patients with aggressive disease.

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Footnote

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

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