Editorial

Moving away (finally) from doublet therapy in lung cancer: immunotherapy and KEYNOTE-189

Sheenu Sheela, Edward S. Kim, Kathryn F. Mileham

Department of Solid Tumor Oncology, Levine Cancer Institute, Atrium Health, Charlotte, NC, USA

Correspondence to: Kathryn F. Mileham. Department of Solid Tumor Oncology and Investigational Therapeutics, Levine Cancer Institute, Atrium Health, 1021 Morehead Medical Dr. suite 3100, Charlotte, NC 28226, USA. Email: kathryn.mileham@atriumhealth.org.

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Treatment of patients with advanced non-small cell lung cancer (NSCLC) has undergone dramatic changes in the recent decade. We have now established a treatment model based on precision medicine: detection of driver mutations and utilization of targeted agents as well as determination of programmed death-ligand 1 (PD-L1) status and integration of immunotherapy. Establishing a diagnosis of advanced NSCLC beyond the histologic subtype by using biomarkers including but not limited to EGFR, ALK, ROS1, BRAF and PD-L1 is the standard of care. However, in patients with adenocarcinoma of the lung, the frequencies of these markers range from 5% to 50% (1). In patients with advanced squamous cell lung cancers, the frequency of driver mutations is less than 5%. Thus, most patients with advanced NSCLC have still been receiving doublet chemotherapy outside of the precision medicine paradigm with treatment regimens based on trials such as ECOG 4599, POINTBREAK, and PARAMOUNT that have modestly improved outcomes (2-5).

Harnessing the immune system opened a new era of therapy in oncology especially in lung cancer. The checkpoint inhibitors FDA approved in lung cancer include nivolumab and pembrolizumab (PD-1 inhibitors), atezolizumab and durvalumab (PD-L1 inhibitors). The initial utilization of PD-L1 expression as a biomarker for immune therapy in lung cancer was limited, given that pembrolizumab was the only FDA-approved agent in the next-line therapy for advanced NSCLC based on PD-L1 expression. Shortly thereafter, the results of KEYNOTE-024 reshaped the first-line assessment and treatment of patients with advanced NSCLC. Pembrolizumab monotherapy was superior to doublet chemotherapy in patients with ≥50% PD-L1 expression within the tumor (6). Most recently, the results of KEYNOTE-042 further supported testing of PD-L1 tumor proportions score (TPS) and using those percentages to determine treatment recommendations.

Data with pembrolizumab in combination with chemotherapy have reshaped our treatment plans for those not eligible for pembrolizumab monotherapy. The phase 2 KEYNOTE-021 study contained a cohort of 123 patients with advanced non-squamous NSCLC with 60 patients receiving pembrolizumab plus carboplatin-pemetrexed and 63 patients receiving chemotherapy alone (7). Objective response rates (ORRs) (primary endpoint) were significantly higher in those who received pembrolizumab with chemotherapy rather than chemotherapy alone (55% *vs.* 29%, P=0.0016). Additionally, patients in the pembrolizumab-chemotherapy arm also experienced improved progression-free survival (PFS) when compared with those who received chemotherapy alone (13.0 *vs.* 8.9 months). Even those with PD-L1 expression less than 1% derived benefit from combination pembrolizumab and chemotherapy interventions. This was the first randomized phase 2 trial in advanced treatment-naïve non-squamous NSCLC to assess and to demonstrate the benefit of

adding immunotherapy to standard of care chemotherapy. Although these results led to FDA recognition of this treatment plan, many clinicians were slow to adopt the regimen while awaiting results of phase 3 randomized data among larger patient populations adequately powered for endpoints including PFS and overall survival (OS).

KEYNOTE-189 was exactly that trial. KEYNOTE-189 was the confirmatory double-blind, phase 3 randomized trial of pembrolizumab-platinum-pemetrexed *vs.* placebo-platinum-pemetrexed as first-line treatment of patients with metastatic non-squamous NSCLC. The primary end points were OS and progression free survival. This trial demonstrated for the first time a significant OS benefit with the addition of immunotherapy to chemotherapy, changing the standard of care in management of these patients while displacing chemotherapy doublets as first-line treatment in those eligible for immunotherapy (8). After 10.5 months of follow-up, the median overall survival (mOS) was 11.3 months in the placebo-chemotherapy arm and not reached in the pembrolizumab-chemotherapy arm. With a hazard ratio for death of 0.49 (P<0.001), there was a 50% improvement in OS. The 12-month OS benefit was noticed in all the 3 subgroups treated with pembrolizumab-chemotherapy, specifically those with PD-L1 expression <1%, 1% to 49%, and ≥50% (61.7%, 71.5% and 73%, respectively) when compared to the placebo-chemotherapy group (52.2%, 50.9% and 48.1%, respectively). Despite a 50% crossover rate (pembrolizumab treatment after progression on the control arm), there was still a very clear survival benefit, suggesting that combination therapy upfront may be better than sequential or later integration of immunotherapy treatment. PFS of 8.8 months was noted in the pembrolizumab-chemotherapy arm *vs.* 4.9 months in the placebo-chemotherapy arm. Similarly, tumor response rates were also significantly improved with the addition of pembrolizumab to platinum-pemetrexed (47.6% *vs.* 18.9%; P<0.001). The results of KEYNOTE-189 are not only practice-changing but also unprecedented. This phase 3 trial of more than 600 patients with advanced non-squamous NSCLC demonstrated improvement in response rate, progression free survival, and OS across all groups of patients, irrespective of PD-L1 expression.

These powerful results also pose challenges in choosing the best first-line therapy for patients with advanced non-squamous NSCLC. Is PD-L1 TPS still relevant as a biomarker to predict the benefit of immunotherapy considering the results of KEYNOTE-189? What treatment recommendation would a clinician give to a patient whose tumor was found to have a TPS ≥50%? Single agent immunotherapy or combination of immunotherapy and chemotherapy? How about in a patient whose tumor has PD-L1 TPS of 40%? What about the biological effect of chemotherapy and sensitivity to immunotherapy?

The KEYNOTE-042 trial was intended to add clarity to this issue of the value of PD-L1 testing and which population should be treated with pembrolizumab monotherapy front-line. KEYNOTE-042 studied pembrolizumab monotherapy *vs.* chemotherapy (carboplatin plus paclitaxel or carboplatin plus pemetrexed) in advanced NSCLC with TPS ≥1%. This study was presented at the 2018 ASCO Annual Meeting and demonstrated significantly improved OS across the entire cohort of patients with TPS ≥1% (16.7 months with pembrolizumab monotherapy *vs.* 12.1 months with chemotherapy). This study categorized patients into groups based on PD-L1 TPS: ≥50%, 20–49%, and 1–19% (note that those with 0% PD-L1 expression were excluded). Median OS in the PD-L1 expression ≥20% group was 17.7 months in the pembrolizumab group and 13.0 months in the chemotherapy group. In the PD-L1 expression ≥50% group, the mOS was 20 months and 12.2 months in the chemotherapy group.

The FDA defines a biomarker as a characteristic that can be measured as an indicator of normal biological processes, pathogenic processes, or responses to an exposure or intervention, including therapeutic interventions. PD-L1 as a biomarker for metastatic lung adenocarcinoma is not without limitations. The marker itself is a quantitative assay and has a range of values from 0% to 100%. The population of patients eligible for front-line monotherapy (PD-L1 tumor proportion score of ≥50%) is approximately 25–30% (9,10). One drawback of using PD-L1 as a biomarker is that it may change with progression of disease or subsequent treatment. There could also be challenges with sampling and testing. There is evidence of enhanced immunogenic effects of chemotherapy with immunotherapy. These include increased cross-presentation of tumor antigen after tumor cell death from chemotherapy (11), reduction in T-regulatory cells, enhancement of dendritic cell activity (8), increase PD-L1 expression on malignant cell (12). These strengthen the arguments for clinicians to utilize the data from KEYNOTE-189. The question of baseline PD-L1 testing for pembrolizumab monotherapy *vs.* no testing and giving combination pembrolizumab with chemotherapy for patients is highly relevant to clinical practice.

The KEYNOTE-189 study provided additional options for patients with advanced non-squamous NSCLC. The

practice of measuring PD-L1 at baseline and treating those patients with TPS ≥50% with pembrolizumab is still clinically valid and safe. For those patients with and TPS ≤50%, chemotherapy with pembrolizumab is a safe and effective option.

The principle of moving away from doublet chemotherapy and moving towards immunotherapy with chemotherapy is also occurring in treatment of patients with advanced squamous cell lung cancer. The first interim analysis results of the KEYNOTE-407, a phase 3 study of chemotherapy with or without pembrolizumab in patients with metastatic squamous cell NSCLC was presented at the 2018 ASCO Annual Meeting. Pembrolizumab plus chemotherapy demonstrated an overall response rate of 58.4% while chemotherapy alone had a response rate of 35%. The duration of response was also significantly improved with the addition of pembrolizumab to chemotherapy (7.7 *vs.* 4.8 months). The median OS was significantly increased from 11.3 months with chemotherapy alone to 15.9 months with the addition of pembrolizumab to chemotherapy (HR =0.64). Median progression free survival was also improved from 4.8 to 6.4 months (HR =0.56). These benefits in both OS and progression free survival were observed irrespective of PD-L1 expression. Similar to the findings in KEYNOTE-189 with non-squamous histologic subtypes, KEYNOTE-407 now demonstrates a new standard of care for the first-line treatment of metastatic squamous cell NSCLC across all levels of PD-L1 expression.

Other studies have been reported and additional studies are in development regarding the utilization of immunotherapy in lung cancer. These studies are not limited to particular histologic subtypes, nor are they limited to advanced stage diseases. The addition of immunotherapy to the treatment paradigm of lung cancer remains in evolution but is also proven to be here to stay.

The treatment of lung cancer has undergone a renaissance in precision medicine over the past two decades with new biomarkers, treatments and indications. How do all the data translate into real-world clinical practice? At this point, the use of doublet chemotherapy should not be a default choice. Biomarker assessments—including PD-L1 expression—at diagnosis for all patients with advanced NSCLC is essential to implement the appropriate therapy. Perhaps future studies will identify better biomarkers to predict the benefit of immunotherapy in patients. Currently, it is appropriate to utilize high PD-L1 expression (≥50%) to treat patients with pembrolizumab monotherapy. For everyone else, strong consideration should be made for combination immunotherapy plus chemotherapy treatment, such as pembrolizumab plus carboplatin-pemetrexed in the advanced non-squamous NSCLC setting.

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Footnote

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

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