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Clinical Lung Cancer
Vol. 20, No. 2, 63-5

Chemo-immunotherapy: The Beginning of a New Era in Lung Cancer

Keywords: Chemo-immunotherapy, KEYNOTE-189, Metastatic lung cancer, NSCLC

Lung cancer is the leading cause of cancer incidence and mortality worldwide, with an estimate of 1.8 million deaths predicted in 2018.[1] Approximately 70% of patients with non–small-cell lung cancer (NSCLC) have locally advanced or metastatic disease at diagnosis.[2] A subset of these patients with an actionable driver mutation will benefit from targeted therapy. For those lacking driver mutations and having a high programmed death-ligand 1 (PD-L1) expression ($\geq$ 50%), pembrolizumab is a preferred treatment option as monotherapy. This is based on the results of the KEYNOTE-024 study, which showed longer progression-free survival (PFS) and overall survival (OS) along with fewer side effects with pembrolizumab as compared with standard chemotherapy.[3] Adenocarcinoma is the most common type of lung cancer. It is also the type of lung cancer with higher driver mutations. As many as 50% to 60% of patients with lung adenocarcinoma can have actionable driver mutations.[4,5] However, a significant number of patients lack driver mutations and high PD-L1 expression; for these patients, platinum-based chemotherapy remains the standard of care. Unfortunately, the efficacy of chemotherapy is modest, with a response rate of approximately 30% to 40% and a median OS of approximately 12 months.[6] There is, therefore, an unmet need for novel treatment strategies in patients with NSCLC without a driver mutation.

Gandhi and colleagues recently reported the results of a double-blind phase III study with chemotherapy in combination with pembrolizumab (KEYNOTE-189 trial).[7] The study included treatment-naive patients with metastatic non-squamous NSCLC without sensitizing EGFR or ALK mutations. A total of 616 patients were randomized in a 2:1 fashion to either receive pembrolizumab (n = 410) or placebo (n = 206) every 3 weeks for up to 35 cycles after standard chemotherapy. All patients received 4 cycles of either cisplatin or carboplatin plus pemetrexed followed by pemetrexed maintenance every 3 weeks.

Submitted: Aug 23, 2018; Revised: Oct 29, 2018; Accepted: Nov 13, 2018; Epub: Nov 22, 2018

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The study showed significant improvement in both the co-primary endpoints in the pembrolizumab arm: median PFS (8.8 months vs. 4.9 months; hazard ratio [HR], 0.52; 95% confidence interval [CI], 0.43-0.64) and estimated OS (69.2% vs. 49.4% at 12 months; HR, 0.49; 95% CI, 0.38-0.64). The survival benefit of combination therapy was evident in all subgroups under consideration, irrespective of age, gender, performance status, smoking status, brain metastases, PD-L1 expression, and type of platinum therapy used.

For patients with PD-L1 $\geq$ 50%, the 1-year OS rate of 73% offered by combination therapy is comparable with the survival benefit offered by pembrolizumab monotherapy in the KEYNOTE-024 trial.[2] Based on this, it seems reasonable to recommend pembrolizumab monotherapy in this subset of patients as the side-effect profile is much better with pembrolizumab alone. However, it will be premature to derive such a conclusion, as the response rate is much higher with combination therapy (61.4% vs. 44.8%). It makes sense to use pembrolizumab monotherapy in those with underlying medical comorbidities and declining performance status and combination therapy in those with good performance status and significant disease burden. However, we should be very cautious on comparing data across trials as it could be confounded by many variables. In the KEYNOTE-024 trial, 18.8% of patients had squamous cell histology, whereas in the KEYNOTE-189 trial, almost all (96%) patients had non-squamous cell histology. Moreover, a higher percentage of patients had brain metastases in the KEYNOTE-189 trial (17% vs. 11%). Awad and colleagues recently reported the outcomes with first-line pembrolizumab for patients with PD-L1 $\geq$ 50% NSCLC. In this retrospective analysis of 172 patients, authors found a significantly higher response rate (45.2% vs. 20.6%; $P = .001$) and longer median PFS (5.3 months vs. 2.5 months; $P = .008$) for patients with PD-L1 expression of 75% to 100% compared with patients with PD-L1 expression of 50% to 74%.[8] We therefore need further prospective studies in defining an optimal cutoff value in selecting patients for first-line PD-1 inhibition monotherapy.

Perhaps the most notable contribution of the KEYNOTE-189 trial is the survival benefit offered by combination therapy for patients with PD-L1 < 50%, including those with PD-L1 < 1%, suggesting the use of combination therapy as a new standard of care in this subgroup. We already know from CheckMate-026 that

1525-7304/$ - see frontmatter
https://doi.org/10.1016/j.cllc.2018.11.006

nivolumab monotherapy does not offer a longer PFS than chemotherapy in patients with a PD-L1 $\geq$ 5%.[9] In addition, Lopes and colleagues recently presented the results of the KEYNOTE-042 study in the annual meeting of the American Society of Clinical Oncology.[10] This phase III study randomized patients with PD-L1 expression > 1% to either receive pembrolizumab or platinum-doublet; it demonstrated a survival benefit in all 3 sub-groups of interest (PD-L1 $\geq$ 50%, $\geq$ 20%, and $\geq$1%) with pembrolizumab. However, the majority (47%) of patients had PD-L1 $\geq$ 50%. Also, there was no difference in OS between the chemotherapy and pembrolizumab monotherapy groups for those with PD-L1 $\geq$ 1% to 49%.

Although survival benefit was demonstrated irrespective of PD-L1 status, the KEYNOTE-189 trial verified that PD-L1 expression remains an independent predictive marker of response to therapy. This result also needs to be viewed in conjunction with growing evidence about tumor mutation burden (TMB) as a predictive biomarker. Recently, Hellman and colleagues reported the result of the CheckMate-227 study, which showed significant PFS benefit with first-line nivolumab plus ipilimumab compared with chemotherapy among patients with NSCLC and high TMB, defined as > 10 mutations/mega base.[11] Additionally, a phase II/III study of use of atezolizumab monotherapy in patients with advanced or metastatic NSCLC with high TMB is ongoing (ClinicalTrials.gov identifier: NCT03178522). Hopefully, this trial will add value to the role that a single-agent checkpoint inhibitor can play in treating patients with high TMB NSCLC.

In the KEYNOTE-189 study, acute kidney injury occurred more frequently in the pembrolizumab arm (5.2% vs. 0.5%), with grade $\geq$ 3 in 8 patients. We do not know the obvious reason for this kidney toxicity yet or whether it was related to chemotherapy (cisplatin or carboplatin) or the combination therapy. The KEYNOTE-189 study also showed slightly more grade $\geq$ 3 adverse events (67.2% vs. 65.8%) along with increased rates of discontinuation of drugs (13.8% vs. 7.9%) in the pembrolizumab arm. An excellent clinical vigilance during post-marketing surveillance is needed to better understand the side-effect profile of combination therapy. Garassino and colleagues reported the pre-specified patient-reported outcome analyses from the KEYNOTE-189 trial utilizing the European Organisation for Research and Treatment of Cancer (EORTC) Quality of Life (QLQ)-C30 and QLQ-LC13.[12] The median time to deterioration in the composite of cough, chest pain, or dyspnea was longer with combination therapy than with chemotherapy, supporting the use of combination therapy.

The KEYNOTE-189 trial was designed to administer maintenance therapy up to 35 cycles until disease progression or unacceptable toxicities. The aim of maintenance therapy is a continued response and to prolong disease stability and thus improve the PFS and OS. In the chemotherapy era, the PARAMOUNT trial showed that pemetrexed maintenance offered a superior survival benefit as compared with placebo.[13] Spigel and colleagues, in the CheckMate-153 trial, investigated the role of maintenance immunotherapy as an exploratory endpoint.[14] Patients were randomized to either receive continuous nivolumab therapy or observation after 1 year of therapy. There was an improvement in PFS and a trend towards improvement in OS in the continued treatment arm favoring continued therapy. We do not have any prospective data on the duration of maintenance therapy for combination therapy. More work is needed to determine the optimum duration of maintenance therapy following combination therapy. Also, can we add pembrolizumab to those subsets of patients who have completed platinum doublet and are currently on pemetrexed? This question remains unanswered by this trial and warrants further study.

Data from the KEYNOTE-407 study echoed a similar finding in treatment-naive patients with metastatic squamous NSCLC. In this double-blind, phase III trial, a total of 559 patients were randomized in a 1:1 fashion to either receive pembrolizumab or saline placebo for up to 35 cycles. As in the KEYNOTE-189 trial, all patients received 4 cycles of platinum-doublet (carboplatin with paclitaxel or nab-paclitaxel). The study shown improved PFS (median, 6.4 months; 95% CI, 6.2-8.3 vs. 4.8 months; 95% CI, 4.3-5.7) and OS (median, 15.9 months vs. 11.3 months; HR, 0.64; 95% CI, 0.49-90.85; $P = .0008$) with combination therapy over chemotherapy in patients with squamous histology.[15]

In summary, the results of the KEYNOTE-189 study showed significant PFS and OS benefit with combination therapy in treatment-naive patients with metastatic non-squamous NSCLC but at the expense of slightly increased toxicity. Taken together with the results of KEYNOTE-407 and IMpower 150, the combination of chemotherapy with immune checkpoint inhibitors should be viewed as a new standard of care for first-line therapy of advanced stage NSCLC.

Disclosure

The author has stated that he has no conflicts of interest.

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