Immune Checkpoint Inhibitors Are Superior to Docetaxel as Second-Line Therapy for Patients With Non-Small Cell Lung Carcinoma

“Our research confirms some prior observations, demystifies some myths, and also identifies new areas of research.”
—Chee Khoon Lee, MBBS (Hons), FRACP, PhD

A new study confirms the value of epidermal growth factor receptor (EGFR) mutation status when choosing immune checkpoint inhibitors versus docetaxel chemotherapy as a second-line treatment of patients with advanced non-small cell lung carcinoma (NSCLC). The meta-analysis, which appears in JAMA Oncology, includes data from 5 clinical trials with a cumulative total of 3025 patients with advanced NSCLC (JAMA Oncol. 2018;4:210-216).

Monoclonal antibodies that block the interaction between the immune checkpoint molecules programmed death protein 1 (PD-1) on immune cells and programmed cell death ligand-1 (PD-L1) have emerged as an important immunotherapy for several forms of cancer. Although these immune checkpoint inhibitors have become the new standard of care for the salvage therapy of patients with advanced stage NSCLC, there is limited information regarding the value of clinical and molecular predictive factors beyond tumor PD-L1 expression. “That’s why we believe that this study breaks new ground,” says lead author Chee Khoon Lee, MBBS (Hons), FRACP, PhD, from the National Health and Medical Research Council Clinical Trials Centre at the University of Sydney in Sydney, New South Wales, Australia.

Eligible randomized controlled trials that compared checkpoint inhibitors with docetaxel in the second-line setting were identified from studies published in English between January 1, 1996, and January 30, 2017. The investigators also searched abstracts from conference proceedings of the American Society of Clinical Oncology, the European Society for Medical Oncology, and the World Conference on Lung Cancer.

“Our research confirms some prior observations, demystifies some myths, and also identifies new areas of research,” says Dr. Lee. “This meta-analysis of 5 well-conducted randomized trials with more than 3000 patient data pooled together helps to address some of these important questions with direct impact on clinical practice and helps to steer future research directions.”

Main Findings

The researchers used a fixed effects inverse variance-weighted method to pool the study results to compare the treatment benefits of checkpoint inhibitors and docetaxel. Tests of interaction were used to assess the differences in treatment effect across subgroups.

In the studies included in this meta-analysis, patients were randomized to receive docetaxel (1338 patients; 44.2%) or 1 of 3 checkpoint inhibitors: 427 patients (14.1%) received nivolumab, 691 patients (22.8%) received pembrolizumab, and 569 patients (18.8%) received atezolizumab. The researchers found that checkpoint inhibitors were associated with prolonged overall survival compared with docetaxel [hazard ratio (HR), 0.69; 95% confidence interval (95% CI), 0.63-0.75 [P < .001]]. Checkpoint inhibitors prolonged overall survival in the EGFR wild-type subgroup (HR, 0.67; 95% CI, 0.60-0.75 [P < .001]) but not in the EGFR-mutant subgroup (HR, 1.11; 95% CI, 0.80-1.53 [P = .54]), and there was a significant interaction between EGFR mutation status and smoking status. Smoking status appears to have minimal effect on the relative efficacy of these 2 therapies.

KEY POINTS

- When compared with docetaxel, checkpoint inhibitors prolong overall survival in second-line and later lines of treatment among patients with advanced NSCLC.
- There was no significant increase in survival noted for patients with EGFR-mutant tumors. Checkpoint inhibitors should be considered for these patients only after all other effective therapies have been tried.
- Smoking status appears to have minimal effect on the relative efficacy of these 2 therapies.
and treatment effect ($P = .005$). The researchers also reported that checkpoint inhibitors prolonged overall survival in the KRAS-mutant subgroup (HR, 0.65; 95% CI, 0.44-0.97 [$P = .03$]) but not in the KRAS wild-type subgroup (HR, 0.86; 95% CI, 0.67-1.11 [$P = .24$]), although the interaction between KRAS mutation status and treatment effect was not statistically significant ($P = .24$).

The relative treatment benefits of checkpoint inhibitors were found to be similar regardless of whether the subjects smoked (never smokers [HR, 0.79] vs ever smokers [HR, 0.69]). "Checkpoint inhibitors significantly prolonged survival for both smokers and nonsmokers as compared to docetaxel chemotherapy," said Dr. Lee. "We believe smoking status should not be used for selection of patients for checkpoint inhibitor therapy." Other factors that demonstrated no noticeable association with the relative benefit of treatment with a checkpoint inhibitor included age (younger than 65 years vs 65 years or older), histology (squamous vs nonsquamous), and sex.

Suresh S. Ramalingam, MD, the Roberto C. Goizueta Distinguished Chair for Cancer Research at Emory University School of Medicine in Atlanta, Georgia, notes that by pooling the data from 5 randomized clinical trials, the researchers were able to report on outcomes for certain clinically relevant subsets of patients. "This information adds to existing knowledge that checkpoint inhibitors are less effective in patients with an EGFR mutation," says Dr. Ramalingam, who also is assistant dean for cancer research and deputy director of the Winship Cancer Institute at Emory.

Dr. Lee added that although patients with NSCLC with KRAS mutations who were treated with a checkpoint inhibitor were found to have a 35% reduction in their risk of dying compared with patients treated with docetaxel chemotherapy, and those without this mutation who were treated with a checkpoint inhibitor had a nonsignificant benefit with checkpoint inhibitors over chemotherapy, this analysis was unable to demonstrate a statistically significant interaction between KRAS mutation status and benefit with checkpoint inhibitor therapy due to limited data regarding KRAS status.

Dr. Lee and his colleagues recommend that patients with EGFR-mutant NSCLC should receive immunotherapy only after other effective therapeutic options have been exhausted, such as EGFR tyrosine kinase inhibitors and chemotherapy. "The role of combination chemotherapy-checkpoint inhibitor treatment warrants further investigation in EGFR-mutant NSCLC patients," he concludes.

**Study Implications**

Dr. Lee explains that this study has important implications for future research. For example, previous studies have found that EGFR and KRAS mutation status is associated with differences in tumor-infiltrating lymphocytes, and that information, together with the results of the current study, might help to guide the development of new treatments and new strategies for personalized treatment decisions.

In addition to their use as a second-line therapy, Dr. Ramalingam notes that checkpoint inhibitors have emerged as first-line therapy for patients with high PD-L1 expression (greater than 50%) for lung cancer, and the US Food and Drug Administration also has approved the combination of chemotherapy plus checkpoint inhibitors as a first-line therapy for patients with advanced stage, nonsquamous NSCLC. However, says Dr. Ramalingam, patients with known treatable mutations such as EGFR, ALK, and ROS1 are not candidates for first-line immunotherapy; instead, "They get targeted therapy."

The overall message, according to Dr. Lee, is that checkpoint inhibitors may be beneficial for some patients. "Ongoing research is still needed of which patients will benefit the most from this class of drug," he says. "PD-L1 testing remains controversial but is the best biomarker we have so far."

doi: 10.3322/caac.21423