Programmed Death-Ligand 1-Rich Premetastatic Niche in Adjuvant Chemotherapy

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The treatment goal for patients with early stage lung cancer is cure. Trial evidence supports the use of cisplatin-based adjuvant chemotherapy (ACT) after surgical resection, especially in stages II and III disease.1 Although ACT is recommended for all patients with stage II to III lung adenocarcinomas, the survival benefit is reportedly limited to 4% to 15% accompanied by side effects,3 and platinum-containing regimens sometimes cause treatment-related death even in favorable-risk patients. In particular, such therapy is not always recommended for elderly patients, who often have comorbidities and may have poor health conditions. The present aging society demands the development of ACT, even for elderly patients, for disease cure, necessitating biomarkers of ACT response. The beneficial effect of ACT is thought to be derived from its targeting of the premetastatic niche, which comprises tumor cells (TCs) and associated immunosuppressive cells.2

Immune checkpoint inhibitors (ICIs), such as monoclonal antibodies against programmed cell death protein-1 (PD-1) or its ligand, programmed death-ligand 1 (PD-L1), are an established treatment modality for lung adenocarcinomas.3 PD-1, which interacts with PD-1 ligands, is primarily expressed after the activation of T cells and suppresses T cell function, causing T cells to fall into a dysfunctional state called exhaustion after chronic antigen stimulation. Therefore, anti–PD-1 or PD-L1 monoclonal antibodies have been found to be effective against various types of cancer, including NSCLC, because they reinvigorate exhausted T cells in the tumor microenvironment (TME). PD-L1 protein expression evaluated by immunochemistry has emerged as a biomarker to select patients with NSCLC for pembrolizumab therapy.1 In this issue of the Journal of Thoracic Oncology, Gross et al.5 investigated the immune status of the TME in 475 patients with stages II to III lung adenocarcinoma with multiplex immunofluorescent staining of immune markers, including PD-L1. The researchers reported that PD-L1 expression in tumors and tumor-associated macrophages (TAMs) was associated with improved survival with ACT. Their findings provide important insights for the future development of combinations with ICIs to be administered in the perioperative period in addition to a predictive biomarker for ACT.

In lung cancer, PD-L1 expression in TCs has been mainly focused on as a predictive biomarker.4 In contrast, PD-L1 in host immune cells (ICs), including antigen-presenting cells (APCs), can also play an important role in antitumor immunity.6,7 Indeed, PD-L1 expression in ICs and TCs could be a predictive biomarker for PD-1 blockade therapies in other types of cancer, such as breast cancer, gastric cancer, and head and neck cancer. Tissue-resident macrophages provide a premetastatic niche for early NSCLC cells,8 and APCs, including macrophages, highly express PD-L1 in the TME.6,7 Thus, such PD-L1–expressing TAMs, which Gross et al.5 focused on, can play important roles in suppressing antitumor immunity and providing a premetastatic niche. Cytotoxic chemotherapy may contribute to immune modulation, such as reduction of immunosuppressive TAMs, as previously reported.9 Thus, patients with PD-L1–expressing TAMs in the TME could obtain a survival benefit from ACT, as Gross et al.5 reported. Another study, however, revealed that cytotoxic chemotherapy could increase PD-L1 expression in TCs and did not decrease but tended to increase TAMs, including PD-L1–expressing TAMs, in the TME of patients with NSCLC who received neoadjuvant cytotoxic chemotherapy.9 Although unpaired samples from different patients who did or did not receive neoadjuvant...
chemotherapies rather than paired samples from the same patients were evaluated in that study, the findings are partially inconsistent with the present study by Gross et al. In addition, there were several differences in patient background between these studies. To elucidate the effect of cytotoxic chemotherapy on PD-L1 expression and TAMs in the TME, further studies should be performed.

The LACE-Bio study analyzed PD-L1 expression in TCs and ICs in patients with early stage NSCLC and, contrary to the results of the present study, concluded that PD-L1 expression is not a predictive biomarker. Nevertheless, there were several differences between the studies. In the LACE-Bio study, one-third of the patients had stage I disease (none of the patients had stage I disease in the present study) and only 41% of the patients had lung adenocarcinoma (100% of the patients had lung adenocarcinoma in the present study). Although the LACE-Bio study investigated PD-L1 expression in all ICs, Gross et al. evaluated PD-L1 expression in TAMs only. These differences can account for the contradictory results. In clinical settings, however, it might be difficult to evaluate PD-L1 expression in TAMs, and we generally evaluate PD-L1 expression in all ICs. In addition, PD-L1 expressed in other APCs, such as dendritic cells, can play important roles in antitumor immunity. Therefore, to use this biomarker, more detailed analyses are warranted.

Recently, adjuvant immunotherapy has been introduced into clinical settings. Adjuvant atezolizumab after ACT in resected stage IB to IIA NSCLC was found to have a disease-free survival benefit compared with the best supportive care. Furthermore, the study of pembrolizumab is ongoing for patients with resected NSCLC treated with or without ACT (KEYNOTE-091, NCT02504372). In addition, several trials of neo-adjuvant immunotherapy combined with cytotoxic chemotherapy followed by surgery are ongoing (AEGEAN [NCT03800134], IMPower030 [NCT03456063], and SQUAT [JapicCTI-195069]) for resectable, locally advanced NSCLC, excluding N3 disease. Given that PD-L1 expression in the TME can be a predictive biomarker for ACT and that PD-1 blockade therapies inhibit the suppressive function of PD-L1, combination with cytotoxic chemotherapy during perioperative settings can enhance the efficacy of adjuvant or neo-adjuvant ICIs. For the SQUAT trial, irradiation was also used as neo-adjuvant therapy in addition to chemotherapy and ICIs, implying the potential promise of such treatment. Nevertheless, there is a concern that perioperative complications may be more frequent. As the balance of efficacy and safety is of importance, the results of that trial are particularly important. Regarding NSCLC with a driver mutation, third-generation EGFR tyrosine kinase inhibitor, were evaluated compared with placebo in resected stage IB to IIA EGFR-mutant NSCLC; the results revealed significantly longer disease-free survival in the treatment group. In addition, a study of the adjuvant agent alecremib, an ALK inhibitor, compared with platinum-based chemotherapy is ongoing for resected stage IB to IIA ALK-positive NSCLC (ALINA, NCT03456076). We have reported that driver genes, including EGF mutations, can influence the TME and that targeted therapies can also improve the immunosuppressive TME. Considering the results of the present study by Gross et al., combination therapies with ACT, molecular targeted therapies, and ICIs during perioperative settings are also of interest. Further investigation of perioperative treatment on the basis of the results of immune profiling and molecular profiling to cure lung cancer is warranted.

**CRediT Authorship Contribution Statement**

**Hiromasa Yamamoto:** Conceptualization, Writing—original draft preparation.

**Yosuke Togashi:** Conceptualization, Writing—original draft preparation, Writing—review and editing.

**References**


