Targeted therapy has revolutionized the treatment landscape of NSCLC-harboring oncogenic driver mutations such as EGFR mutation and anaplastic lymphoma kinase (ALK) rearrangement. In preclinical models, both EGFR-mutant and ALK-rearranged tumors are reported to induce up-regulation of programmed cell death ligand 1 (PD-L1) expression, possibly as an adaptive immune escape mechanism.\(^1\)-\(^3\) A retrospective clinical study has shown that high PD-L1 expression is a poor response predictor for EGFR-mutant patients with NSCLC treated with EGFR tyrosine kinase inhibitors (EGFR TKIs).\(^4\) In addition, the study has shown that approximately half of the patients (7/15) with de novo resistance to EGFR TKIs have high PD-L1 expression in the tumor and enriched CD8\(^+\) T cells in the tumor microenvironment, indicating that at least a subset of patients with NSCLC with driver oncogenes could potentially benefit from treatment with immune checkpoint inhibitors (ICIs). Despite encouraging evidence supporting the use of anti–PD-L1 therapy in NSCLC-harboring oncogenic mutation, the efficacy results were disappointing. The objective response rate (ORR) for ICI monotherapy in EGFR-mutant or ALK-positive patients was far from satisfactory in comparison with that observed in their wild-type counterparts.\(^5\)

Many argue that the failure of anti–PD-L1 monotherapy could be partly explained by the presence of a substantial lower mutation load and, hence, lower neoantigen load in oncogene-addicted tumors. Some suggest that treatment with a targeted agent would enhance antitumor immunity by increasing neoantigens from triggered tumor-cell death and by further downregulating PD-L1 expression, providing a biological rationale for combinational use of targeted agents and ICIs.\(^7\)

In this issue of the *Journal of Thoracic Oncology*, Felip et al.\(^6\) present the safety and activity results of a phase Ib trial using combination therapy with ALK inhibitor ceritinib plus nivolumab in 36 patients with ALK-rearranged NSCLC. Four of 12 patients being evaluated in the 450-mg cohort had dose-limiting toxicity (DLT) with transaminitis. Grade 3 or 4 adverse events (AEs)—mainly skin rash and elevated levels of aspartate transaminase and/or alanine aminotransferase and lipase—were observed more frequently in comparison with either ceritinib or nivolumab monotherapy. No treatment-related interstitial lung disease (ILD) was reported in the study. The ORR was comparable to that observed in patients treated with ALK-TKIs alone (without ICIs). To further evaluate how the PD-L1 expression level correlated with treatment efficacy, the authors conducted an analysis based on the positivity of PD-L1 expression. Although the results were only exploratory owing to the small number of patients, the ORR in PD-L1-positive patients was numerically higher than in PD-L1-negative patients at every cutoff (1\%, 5\%, and 10\%), suggesting that PD-L1 expression may be a potential selection biomarker for combination therapy.

The study reported by Felip et al.\(^6\) is among several clinical trials conducted to evaluate combination therapy with TKIs and ICIs. However, before any response or survival benefit could be shown clearly, alarming safety signals, including severe ILD and transaminitis, had already surfaced. In TATTON (NCT02143466), a phase Ib study of osimertinib plus durvalumab for EGFR-
mutant NSCLC, an unexpectedly high incidence of ILD (13 of 34 patients had ILD, and five of them were grade 3 or 4) was observed, leading to early termination of this cohort. In CAURAL (NCT02454933), a phase III study to investigate osimertinib plus durvalumab combination therapy versus osimertinib monotherapy in patients with T790M-positive advanced NSCLC, the safety results were slightly less concerning compared with those of the TATTON trial, with one of 12 patients who received the combination treatment developing a grade 2 ILD 63 days after one dose of durvalumab. Nevertheless, the CAURAL trial too was terminated prematurely because of safety concerns regarding osimertinib plus durvalumab combination therapy from the TATTON study. In a retrospective analysis, the sequential treatment with durvalumab followed by osimertinib was associated with severe immune-related AEs in six of 41 patients with ILD, hepatitis, or colitis. The treatment sequence seemed to be critical because treatment in the reverse sequence (osimertinib followed by durvalumab) did not result in a higher level of toxicity in comparison with treatment with either drug administered alone. Similar results were reported in an observational study showing increased risk of interstitial pneumonitis in patients receiving combination treatment of EGFR TKIs and nivolumab (18 of 70 patients). Fifteen of 18 incident cases had identifiable treatment sequences—EGFR TKIs were administered after nivolumab—further highlighting the association of treatment sequence in the development of ILD. The high incidence of ILD when EGFR TKIs were added after ICIs may be related to the prolonged effect of receptor occupancy by ICIs. It is notable that no excess toxicity was observed in either sequential or combination use of erlotinib and ICIs. In KEYNOTE-021, an open-label, multicohort, phase I study, five of seven patients (71.4%) receiving concurrent gefitinib and pembrolizumab developed grade 3 or 4 liver toxicity with transaminitis. On the other hand, pembrolizumab plus erlotinib was associated with manageable skin rash and an ORR of 41.7%. In patients with a PD-L1 tumor proportion score of 50% or more—a predictive marker of poor response to treatment with EGFR TKIs—the ORR after treatment with erlotinib plus pembrolizumab was 100% (4/4) and durable. The TKI-ICI combination appears to be useful in overcoming short progression-free survival observed in patients with EGFR mutations whose tumors also express high PD-L1. However, these findings should be interpreted with caution owing to the small sample size. Further exploration with this combination in a biomarker-enriched patient group will be noteworthy.

Likewise, a combination strategy with targeted therapy and anti-PD-L1 antibody has been attempted in ALK-rearranged NSCLC. In group E of CheckMate 370 (NCT02393625), five of 13 patients (38.5%) treated with crizotinib plus nivolumab developed grade 3 or 4 hepatic toxicities, and two of these five patients died at least partly owing to treatment-related AEs. Subsequently, all ongoing combination treatments in the study were permanently discontinued. In comparison, a phase Ib study evaluating alectinib plus atezolizumab in treatment-naive patients with ALK-rearranged NSCLC found a manageable AE profile (52.4% of patients developed treatment-related grade 3 AEs; no DLT was observed) and comparable efficacy with alectinib monotherapy (progression-free survival 21.7 mo). The AE profile of ceritinib plus nivolumab was less severe than that seen in group E of CheckMate 370 but more concerning than that of alectinib plus atezolizumab. As a result, the safety committee, aiming to reduce the toxicity and to allow for safety observation, decided to investigate an alternative dosing regimen.

Given that TKI monotherapy is very effective with a high response rate in EGFR-mutant and ALK-rearranged patients, the main goals of treatment with the TKI-ICI combination are to increase the response duration and to overcome primary resistance to TKI monotherapy. However, all attempts, including the study published in this issue by Felip et al., have failed to achieve these objectives. On the basis of what we have learned from previous experiences, it is evident that an all-comer design in combination trial with targeted therapy and anti-PD-L1 antibody is no longer justified owing to significantly increased toxicity without clinically meaningful benefit. However, the small number of patients in these studies prevents us from rejecting the possibility that combination therapy may be beneficial for a yet-to-be-defined small population of patients. The combination approach is still worthy of investigation, but integration of well-characterized predictive biomarkers is mandated to provide the most rational enrichment strategy to select patients who benefit the most from combination therapy. How to choose the right predictive biomarkers will still be an active area of investigation. The candidate biomarkers include, but are not limited to, PD-L1 expression and CD8+ T-cell infiltration. In addition, targeted agents associated with less toxicity in combination with ICIs in prior studies, such as erlotinib or alectinib, should be preferentially considered as the combination partners. We anticipate that further understanding of dynamic changes of the tumor-immune microenvironment in response to treatments would provide clinicians valuable insights in selecting the most appropriate research strategy in the area of immunoncology for patients with NSCLC with oncogenic driver mutations.
References