Editorial Commentary

Concerns and controversies regarding ipilimumab-based immunotherapy in the first-line treatment of non-small cell lung cancer

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Ipilimumab is a fully human monoclonal antibody against cytotoxic T-lymphocyte antigen 4 (CTLA-4), which has shown early evidence of longer overall survival (OS) in patients with melanoma (1), renal cell carcinoma (2), and unresectable malignant pleural mesothelioma (3). Furthermore, ipilimumab plus nivolumab has shown antitumor activity in patients with small-cell lung cancer (4).

The ipilimumab-based immunotherapy as a first-line treatment of non-small cell lung cancer (NSCLC) has represented a substantial change in therapeutics, particularly for patients with potential low tolerability to conventional chemotherapy. Yet, the extended long-term survival is achieved only in a minority of patients with NSCLC (5-7).

Dual checkpoint blockade was associated with durable tumor responses and prolonged survival in patients with advanced NSCLC; however, a higher frequency of adverse events (AEs) was reported with the dual immunotherapy regimen (5,6,8,9).

Most of the evidence regarding the development of ipilimumab-based immunotherapy in the first-line treatment of advanced NSCLC derives from two pivotal clinical trials; CheckMate-227 (5) and CheckMate-9LA (6). CheckMate-227 is a randomized, first-line, open-label, phase 3, multi-part trial that explored the efficacy and safety of nivolumab plus ipilimumab, compared with platinum-doublet chemotherapy (5). Eligible participants included patients with squamous or nonsquamous stage IV or recurrent NSCLC. CheckMate 227 is a six-arm trial, divided into two parts. In part 1a, patients with programmed cell death-1 ligand-1 (PD-L1) expression level ≥1% on tumor cells (TCs) were randomly assigned in a 1:1:1 ratio to receive nivolumab [at a dose of 3 mg per kilogram (kg) every two weeks] plus ipilimumab (at a dose of 1 mg per kg every six weeks) *vs.* nivolumab monotherapy (240 mg every two weeks) *vs.* platinum doublet chemotherapy (every three weeks for up to 4 cycles). Patients whose tumor express PD-L1 <1% were allowed to enroll in the part 1b of the study. Crossover between the treatment groups was not permitted. The primary endpoint was OS (5).

A total of 1,189 patients were enrolled in part 1a; 396 were assigned to receive nivolumab plus ipilimumab, 396 to nivolumab monotherapy, and 397 to chemotherapy. Of the 550 patients enrolled in part 1b, 187 were assigned to receive nivolumab plus ipilimumab, 177 nivolumab plus chemotherapy, and 186 chemotherapy. Three-year update from CheckMate-227 part 1 (at a median follow-up of 43.1 months), patients with PD-L1 level ≥1% on TCs showed a survival benefit compared to the chemotherapy arm (HR: 0.79; 95% CI, 0.67–0.93); three-year OS rates were 33% for nivolumab plus ipilimumab and 22% for the chemotherapy alone arm (10). Nivolumab plus ipilimumab also delayed disease progression among these patients, with a three-year progression-free survival (PFS) rate of 18% with the combination of ICI *vs.* 4% with chemotherapy alone. 38% of patients with PD-L1 level ≥1% on TCs who responded to nivolumab plus ipilimumab continue therapy at year three *vs.* 4% in the chemotherapy arm. In patients whose tumors expressed PD-L1 <1%, the OS rate at year three for nivolumab plus ipilimumab arm was 34% compared to 15% for chemotherapy alone (HR: 0.64;

95% CI, 0.51 to 0.81); moreover, benefits in PFS were also observed in those patients in the nivolumab plus ipilimumab arm 13% *vs*. 2% in the chemotherapy arm at 3 years. The response rate in the nivolumab plus ipilimumab arm was 34% *vs*. 0% in the chemotherapy alone arm (10).

The third-year outcomes from CheckMate-227 provided evidence of the survival benefits of the nivolumab plus ipilimumab combination in the first-line setting for patients with advanced NSCLC (10) when compared to platinum-double regimens. The sustained responses observed confirmed the scientific rationale that dual inhibition of PD-1 and CTLA-4 could increase the immune response and provide long-term benefits. This trial led to the FDA to the approval of ipilimumab plus nivolumab as first-line therapy for patients with recurrent NSCLC whose tumors express PD-L1 (≥1%) (7). Albeit the relative benefit of nivolumab plus ipilimumab, compared with chemotherapy, was numerically higher in patients with PD-L1 expression level <1% on TCs, FDA approval was limited to NSCLC with PD-L1 ≥1% since the primary OS endpoint analysis for nivolumab+ipilimumab versus chemotherapy was restricted to this cohort (5)

It is important to mention that the comparison arms in these trials were platinum-based chemotherapies without ICI, which are no longer the standard of care for first-line metastatic NSCLC (11,12).

CheckMate-9LA; a randomized, international, phase 3 trial evaluated ipilimumab-based immunotherapy combined with a limited course of chemotherapy (6). The study included patients with histologically confirmed advanced NSCLC, who had not received previous treatment and without known sensitizing EGFR/ALK alterations. Patients were randomized 1:1 to nivolumab (360 mg every three weeks) plus ipilimumab (1 mg/kg every six weeks) plus chemotherapy (2 cycles) and chemotherapy alone. Groups were stratified by PD-L1 expression level (<1% *vs*. ≥1%). A total of 361 patients were enrolled in the ipilimumab, nivolumab plus chemotherapy group, and 358 in the chemotherapy alone group. At 12.7-month follow-up, the experimental group showed significant OS benefit *vs*. the chemotherapy arm (15.6 *vs*. 10.9 months, respectively; HR: 0.66; 95% CI, 0.55–0.80); with improvements in PFS (6.8 *vs*. 5.0 months, respectively; HR: 0.70; 97.48% CI, 0.57–0.86; P<0.0001) and a better objective response rate (ORR) (38% *vs*. 25%, respectively; P<0.0003).

Clinical benefit in terms of median OS was consistent across all PD-L1 levels subgroups and histological subtypes. However, the immunotherapy combination with chemotherapy may have lower efficacy than chemotherapy alone in patients >75 years and never smokers based on a subgroup analysis (HR: 1.21 and HR: 1.14, respectively) (6).

The comparison of ipilimumab, nivolumab plus 2 cycles of chemotherapy with ipilimumab plus nivolumab alone (6); makes it difficult to determine the benefit ipilimumab brings to the regimen precisely. The combination of ipilimumab plus nivolumab was shown to improve OS when compared with. chemotherapy alone in first-line advanced NSCLC in CheckMate 227 part 1, regardless of PD-L1 expression. Therefore, the rationale behind the CheckMate-9LA was that a limited course of chemotherapy combined with nivolumab plus ipilimumab could provide rapid disease control while building on the durable OS benefit seen with the dual PD-1 and CTLA-4 inhibition (6). These studies were designed to analyze the role of combination immunotherapy with or without chemotherapy, but not the role of adding ipilimumab. Understanding the limitations of cross-trial comparisons, *Table 1* summarized the findings from CheckMate-227 part 1 and CheckMate-9LA. The data should be cautiously interpreted, considering the differences in patients' characteristics at baseline and chemotherapy regimens (6).

When comparing toxicity profiles, CheckMate-227 part 2 reported that 45% of patients treated with nivolumab and chemotherapy suffered a treatment-related grade 3–4 AEs (13), while the CheckMate-9LA showed that 47% of patients on the ipilimumab, nivolumab plus chemotherapy treatment had the same grade of AEs reported (6). Besides, it is challenging to determine if this regimen is more tolerable than triple therapy with chemotherapy plus one ICI, but it certainly offers treatment options for patients with end-organ damage (14,15).

Challenges of combination immunotherapy related toxicities

The combination of ICI is associated with a higher risk of grade 3–4 AEs and a marginally larger risk of all-grade AEs than ICI monotherapy (16). Among patients with advanced NSCLC enrolled in CheckMate-012, a two open-label, phase 1, multi-cohort trial, lowering the ipilimumab dose to 1 mg/kg of body weight every six weeks lead to a better safety profile than other ipilimumab-based regimens without compromising efficacy (8,17).

CheckMate-227 part 1 trial reported treatment-related

Table 1 Comparison between patients' groups treated with ipilimumab-base immunotherapy from CheckMate-227 part 1 and CheckMate-9LA

Variables	CheckMate-227 part 1 (5)		Checkmate-9LA (3)	
	Ipilimumab + nivolumab	Chemotherapy alone	Ipilimumab + nivolumab + chemotherapy	Chemotherapy alone
Age (median)	64 [26–87]	64 [29–87]	65 [35–81]	65 [26–86]
Sex %				
Male	67.4	66.0	70%	70%
Female	32.6	34.0	30%	30%
Smoking status %				
Never smoked	13.6	13.4	13%	14%
Current or former smoker	85.2	85.6	87%	86%
Tumor histologic type %				
Squamous	28.0	27.8	31%	31%
Nonquamous	71.9	85.6	69%	69%
PD-L1 status %				
<1%	32.1	31.9	40%	39%
≥1%	67.9	68.1	60%	61%
1–49%	32.8	35.2	38%	32%
≥50%	35.2	32.9	22%	29%
mOS	17.1 mo*	13.9 mo*	15.6 mo	10.9 mo
mPFS	7.2 mo**	5.5 mo**	6.8 mo	5.0 mo

*, results from the group with tumor PD-L1 expression level <1%. **, 1-year PFS, only assessed in patient with high tumor mutational burden. mOS, median overall survival; mPFS, median progressive-free survival; PD-L1, programmed cell death-1 ligand 1; mo, months.

Table 2 Comparison of treatment-related adverse events between patients' groups treated with ipilimumab-base immunotherapy from CheckMate-227 part 1 and CheckMate-9LA

Variables	CheckMate-227 part 2 (5)		Checkmate-9LA (3)	
	Nivolumab + ipilimumab	Chemotherapy alone	Ipilimumab + nivolumab + chemotherapy	Chemotherapy alone
Any grade	77%	82%	92%	88%
Grade 3/4	33%	36%	47%	38%

AEs of any severity grade in 77% of patients treated with nivolumab plus ipilimumab and 82% with chemotherapy. Grade 3–4 treatment-related AEs were observed in 33% of patients on combination ICI and in 36% of patients undergoing chemotherapy (*Table 2*) (10). Additionally, the CheckMate-9LA trial showed that any grade AEs were more common with ipilimumab, nivolumab, and chemotherapy than the chemotherapy alone regimen (92% *vs.* 88%), and higher frequency of therapy discontinuation (19% *vs.* 7%, respectively) (*Table 2*) (6). The most frequent AEs were nausea, anemia, asthenia, and diarrhea (≥15%). In ChechMate-9LA Grade 3–4 treatment-related AEs were present in 47% of patients in the experimental group compared with 38% in the chemotherapy arm. AEs with potential immunology etiology were skin-related (40%), endocrine (26%), and gastrointestinal events (23%). Yet, no new safety signals were reported (6). The safety profile of these new combination regimens should be taken into account when deciding the best first-line regimen for newly diagnosed patients with NSCLC.

Role of tumor mutational burden (TMB) as an immunotherapy combinations biomarker in advanced NSCLC

There is a need for predictive biomarkers to identify patients with untreated metastatic NSCLC who may benefit from new therapies, particularly as the options for immune inhibition continue to expand (18). One emerging biomarker of response to anti-PD-1 therapy is TMB (i.e., the total number of mutations per coding area of a tumor genome) (19,20). CheckMate-568 trial, a phase 2 study involving patients with NSCLC treated with nivolumab plus ipilimumab, established an effective cut-off of TMB ≥10 mutations per megabase (Mb) for selecting patient most likely to have a response, independently of tumor PD-L1 expression level (20).

In Checkmate-227 part 1a; a biomarker analysis was performed on 1,739 randomly assigned patients; of the 1,004 patients whose TMB could be evaluated across all treatment groups, 444 (44.2%) had ≥10 mutations per Mb (high TMB), including 139 patients assigned to nivolumab plus ipilimumab and 160 patients assigned to chemotherapy (18). Among patients with high TMB, 24.4% of the ones treated with nivolumab plus ipilimumab, and 3.1% treated with chemotherapy were continuing treatment at the time of database analysis. Subgroup analysis among patients with a high TMB according to PD-L1 status showed that PFS was longer with nivolumab plus ipilimumab than chemotherapy alone among patients with a PD-L1 expression level ≥1% on TCs (HR: 0.62; 95% CI, 0.44–0.88) and those with a level <1% (HR: 0.48; 95% CI, 0.27–0.85). The benefit of combined immunotherapy was durable, with 43% of patients being progression-free at year one *vs*. 13% in the chemotherapy arm (18).

The combination of ipilimumab plus nivolumab may represent an effective treatment regimen for patients with high TMB (18,20). Moreover, TMB and PD-L1 expression were independent factors in predicting the efficacy of ICIs (18). Currently, TMB remains a controversial tissue-based biomarker for immune checkpoint blockade as some studies have inconsistently shown predictive values (21). Certainly, the diverse cut-off values adopted may explain the heterogeneity of these results (21). Besides, owing to the huge cost and complexity of sequencing, some challenges need to be addressed before using TMB as a routine clinical practice biomarker (21). The initial method developed to assess TMB is whole-exome sequencing (WES) using next-generation sequencing (NGS). However, this technique is costly and requires excessively lengthy turnaround times making it unsuitable for large-scale and routine clinical applications (22). In contrast, targeted NGS panels, either in tissue or blood, has since been used in clinical practice to estimate TMB. Different commercial panels feature different bioinformatic protocols and different filtering methods, e.g., to account for germline mutations, etc.) (22). Nevertheless, TMB determination in tissue requires a sufficient quantity of tissue usually obtained through core biopsies, and if the testing is not initially requested results can be delayed (14 days or more), patients may have limited availability of tumor samples; thus, the approach of tissue acquisition needs to be determined early in the process (23). Additionally, TMB testing is dependent on characteristics of the specific tumor focus tested for a patient (e.g., primary *vs*. metastatic) and the testing platform used for the detection; therefore, observed TMB results may vary between different specimens from the same patient and within detection methodologies employed on the same sample (24). Currently, FoundationOne is the first FDA-approved tissue-based broad companion diagnostic that is clinical and analytically validated for TMB testing with a successful determination of TMB expected for 80% to 95% of patients undergoing testing (24). Increasing uptake of TMB as a predictive biomarker in the clinic creates an urgent need to bring stakeholders together to agree on the harmonization of key aspects of panel-based TMB estimation. These harmonization efforts should improve the consistency and reliability of panel TMB estimates and aid in clinical decision-making (25).

Several factors regulate immunotherapy responses, therefore, establishing prognostic and predictive biomarkers is crucial to determine which patients with advanced NSCLC will benefit from dual immunotherapy. Certainly, high TMB is an important biomarker in advanced NSCLC, yet refinement of interpretation and contextualization is needed. Other biomarkers to better predict responders to immunotherapy among patients with NSCLC are under investigation (e.g., tumor-infiltrating lymphocytes, microsatellite instability-H/mismatched repair-deficiency, *PTEN* gene, *STK11* gene deletion/LKB1 kinase mutation) (26).

Risk of hyperprogressive NSCLC under ipilimumab-based regimens

Hyperprogressive disease (HPD) is an aggressive pattern of progression reported for patients treated with PD-1/PD-L1 inhibitors (27,28). An increase of the tumor kinetics and poor

survival are characteristics expected with HPD (28). However, the use of different definitions of HPD introduces the risk of describing different tumoral behaviors (28). A multicenter cohort study investigated the development of HPD in patients with advanced NSCLC treated with PD-1/PD-L1 inhibitors compared with single-agent chemotherapy (27). Hyperprogression was defined as disease progression at first evaluation, with a change in tumor growth rate (TGR) exceeding 50%. Overall, 406 patients with advanced NSCLC were included. In the immunotherapy cohort, 13.8% (n=56) were classified as hyperprogressors *vs.* 5.1% (n=3) observed in the chemotherapy cohort. Patients experiencing HPD within the first six weeks of PD-1/PD-L1 inhibitor treatment had significantly lower OS (3.4 months; 95% CI, 2.8–7.5) compared with patients with traditional progressive disease (6.2 months; 95% CI, 5.3–7.9) (HR: 2.18; 95% CI, 1.29–3.69; P=0.003) (29).

Although HPD is a controversial topic, this study suggested that this phenomenon is more common with PD-1/PD-L1 inhibitors compared with chemotherapy in pretreated patients with NSCLC. Moreover, there are individual somatic mutations and mutation clusters associated with clonal evolution that may contribute to the accelerated tumor growth observed in HPD (29). Thus, clinicians should be aware of this condition to properly guide the decision-making.

Choice of first-line treatment: Ipilimumab-base immunotherapy *vs.* pembrolizumab

Nivolumab and pembrolizumab were the first immune checkpoint inhibitors showing meaningful survival benefits in patients with NSCLC after disease progression to cytotoxic therapy (30). Since 2018, ICIs have been incorporated into first-line therapy in combination with chemotherapy (6,10). Currently, there are multiple immunotherapy options for patients with advanced NSCLC, therefore, individual and tailored discussion with patients and caregivers need to take place before a treatment plan is decided.

A pooled analysis included a total of 2,372 patients from three randomized trials (KEYNOTE-024, KEYNOTE-042, and CheckMate-227) (31). Patients with tumor PD-L1 expression level ≥1% had improvement of OS relative to chemotherapy in both nivolumab plus ipilimumab (HR: 0.82; 95% CI, 0.69–0.97) and pembrolizumab groups (HR: 0.81; 95% CI, 0.71–0.93). However, the combination of nivolumab and ipilimumab was not superior to pembrolizumab in terms of OS (HR: 0.98; 95% CI, 0.77–1.24) and ORR (RR: 1.17; 95% CI, 0.89–1.52). In contrast, nivolumab and ipilimumab significantly improved PFS (HR: 0.79; 95% CI, 0.65–0.96) when compared with pembrolizumab (HR: 1.07; 95% CI, 0.94–1.21). Analyses of treatment-related AEs showed that the rate for all grades [relative risk (RR): 1.28; 95% CI, 1.17–1.40] and ≥ grade 3 (RR: 2.18, 95% CI, 1.7–2.8) were significantly higher with nivolumab plus ipilimumab as compared with pembrolizumab. This pooled analysis suggested that both regimens provided comparable OS benefit for patients with PD-L1-positive NSCLC, but nivolumab plus ipilimumab conveyed a less favorable toxicity profile (31). Another major aspect of between-group comparison is the lack of data about 5-year survival rates of the combination of nivolumab and ipilimumab in advanced NSCLC.

Conclusions

NSCLC remains a complex and challenging disease with limited OS, despite recent immunotherapy advances. Patients remain in need of additional options that may provide a long-lasting survival benefit and acceptable quality of life. Current evidence from CheckMate-227 and ChecMate-9LA showed survival gains with nivolumab plus ipilimumab in the first-line treatment of NSCLC and reiterate the scientific rationale that dual inhibition of PD-1 and CTLA-4 has the potential to deliver durable responses for this population of patients. Decision-making should be centered on patients' preference and their own risk of tolerance. We look forward to further research to establish the effectiveness of ipilimumab within a dual immunotherapy approach and to provide a safer profile for our patients.

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