Editorial Commentary

CheckMate 227 trial has not checked the immune-strategy in first-line setting in advanced non-small cell lung cancer

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Immune checkpoint inhibitors (ICIs) are the new standard cornerstone therapeutic strategy in first-line setting of advanced non-small cell lung cancer (NSCLC) patients without oncogenic driver. This new therapeutic approach is based on the significant survival benefit with ICIs (either as monotherapy in tumors with high PD-L1 expression (1,2) or in combination with chemotherapy regardless of PD-L1 expression or histology subtype (3,4) compared with the standard platinum-based chemotherapy. Similarly, combination of ICIs has already reported overall survival (OS) improvement in other malignancies, such as melanoma or renal cell carcinoma, and more recently in advanced NSCLC with outcome data coming from the combination of nivolumab and ipilimumab in first-line setting in the randomised phase III CheckMate 227 trial (5,6).

The eagerly awaited results from CheckMate 227 trial came after several major amendments, and finally the trial assessed two co-primary endpoints, the progression free survival (PFS) in tumors with high tumor mutational burden (TMB) defined as ≥10 Mutations/megabase, Mut/Mb, and the OS in PD-L1 ≥1% population with the ICI combination compared with platinum-based chemotherapy. In patients with tumors carrying high TMB (n=299, 18% of all patients with tumor samples available to attempt TMB) nivolumab and ipilimumab significantly prolonged the PFS compared with chemotherapy (7.2 *vs.* 5.5 months, hazard ratio, HR 0.58, 75% confidence interval, 5% CI: 0.41–0.81). However, risk of early progression (≤3 months after treatment initiation) was higher in ICI combination than in chemotherapy arm despite patients being selected according to a predictive biomarker (5). The coprimary OS endpoint was also met, and longer survival was reported in nivolumab plus ipilimumab arm compared with chemotherapy arm (17.1 *vs.* 14.9 months, HR 0.79; 95% CI: 0.65–0.96, P=0.007), but was not significant in the subgroup of never–smokers or patients with liver metastases. Indeed, the risk of early death was higher in ICI arm. Of relevance, the survival benefit with nivolumab plus ipilimumab combination occurred regardless of PD-L1 expression (PD-L1 <1%: HR 0.62, 95% CI: 0.49–0.79; PD-L1 ≥1%: HR 0.79, 95% CI: 0.65–0.96; PD-L1 1–49%: HR 0.94, 95% CI: 0.75–1.18; and in PD-L1 ≥50%: HR 0.70, 95% CI: 0.55–0.90) or TMB cut-off (TMB ≥10 Mut/Mb: HR 0.68, 95% CI: 0.51–0.91; and TMB <10 Mut/Mb: HR 0.75, 95% CI: 0.59–0.94). These results question the role for TMB as predictive biomarker for ICI combination, and suggest that the maximum OS benefit observed in PD-L1 ≥1% tumors is mainly driven by the subgroup of tumors with high PD-L1 expression (PD-L1 ≥50%) (6).

Although the CheckMate 227 trial reported a significant survival benefit with ICI combination, the potential role of this strategy in the first-line setting in the current standard therapeutic approach is questionable. Both co-primary endpoints were achieved with a control arm

that now seems suboptimal based on recent survival data with immune-chemotherapy combination. In the PD-L1 ≥50% subgroup, nivolumab plus ipilimumab achieves the maximum benefit (HR 0.70, 95% CI: 0.55–0.90). However, it remains unknown whether ICI combination in this population really improves the OS compared with monotherapy either with an anti-PD1 [KEYNOTE 024 (1) with pembrolizumab, HR 0.65, 95% CI: 0.50–0.86] or with an anti-PD-L1 [IMpower110 (2) atezolizumab, HR 0.59; 95% CI: 0.40–0.89]. Both single-agents have reported similar survival benefit compared with ICI combination, even despite the higher crossover-rate (e.g., 65% in KEYNOTE024 trial compared with crossover rate not allowed in the CheckMate 227 trial, however, 43% of patients in chemotherapy arm received subsequent ICI at progression). Indeed, in the prespecified analysis in the subgroup of tumors with PD-L1 ≥50% from CheckMate 227 trial, nivolumab plus ipilimumab did not increase PFS (HR 0.80, 95% CI: 0.64–1.01) or OS (HR 0.87, 95% CI: 0.68–1.12) compared with single-agent nivolumab, but the combination was more toxic (grade ≥3 adverse events: 33% *vs.* 19%). However, these results should be considered descriptive. Therefore, the safety/efficacy ratio along with the economic impact are relevant before broadly accepting the ICI combination over monotherapy in this population with high PD-L1 expression, and single agent remains the standard of care. The ongoing phase III KEYNOTE 598 trial (NCT03302234) comparing pembrolizumab plus ipilimumab versus single-agent pembrolizumab in PD-L1 ≥50% may help to answer this question.

In the subset of PD-L1 negative tumors from the CheckMate 227 trial, an exploratory analysis reported a stronger survival benefit with nivolumab plus ipilimumab compared with chemotherapy (6). All together may suggest a potential strategy of ICI combination in PD-L1 negative tumors. However, the ICI combination should be compared to the approved combinations, in particular chemotherapy plus pembrolizumab. This is of relevance as contrary to data from other phase III clinical trials (3,4), the combination of nivolumab plus chemotherapy did not improve the OS compared with chemotherapy in PD-L1 negative tumors (HR 0.78; 95% CI: 0.60–1.02), which was a secondary endpoint of the CheckMate 227 trial (6). Similarly, in the part 2 of the CheckMate227 trial, assesing the addition of nivolumab to first-line platinum-based chemotherapy did not meet the primary endpoint of OS benefit in treatment-naïve patients with non-squamous histology compared with chemotherapy alone (7). The CheckMate 227 trial did not directly compare the OS between nivolumab and ipilimumab versus nivolumab plus chemotherapy in PD-L1 negative tumors. Although nivolumab plus chemotherapy reported higher response rate than nivolumab plus ipilimumab combination (38% *vs.* 27%) in PD-L1 negative tumors, and depth of response rate on ICI has been associated with greatly improved outcomes (8,9), it was not translated in a survival benefit with similar 1-year (59% *vs.* 60%) and 2-year (35% *vs.* 40%) overall survival. All these data in absence of a randomized clinical trial only suggest a similar efficacy between ICI combination and immune-chemotherapy combination in PD-L1 negative tumors. However, immune-chemotherapy combination with pembrolizumab remains the standard of care in this population regardless the histology (3,4), and it remains unknown whether the addition of an anti-CTLA4 has any dominant effect in PD-L1 negative tumors. Finally, the efficacy of nivolumab monotherapy versus chemotherapy was also assessed as a prespecified endpoint in the CheckMate 227 trial. Nivolumab did not improve the OS over chemotherapy neither in the PD-L1 ≥1% nor in the PD-L1 ≥50% subgroup, similar to previous data reported (10).

In the era of precision medicine, research of predictive biomarkers for ICI is a current challenge. Contrary to CheckMate 026 trial (10), that showed in an exploratory analysis that combination of 2 biomarkers (high PD-L1 expression and high TMB) may identify those patients who obtained the maximum benefit of ICI; in the CheckMate 227 trial, combining the same two key biomarkers did not identify a subgroup with an increased magnitude of benefit with nivolumab plus ipilimumab over chemotherapy, although the sample sizes was modest for this analyses. Therefore, just PD-L1 expression remains the gold-standard predictive biomarker in first-line setting, and this biomarker should not be avoided in daily clinical practice. Despite the fact that CheckMate 227 trial endorses upfront combination of ipilimumab and nivolumab in all-comers suggesting that PD-L1 status would not be necessary, PD-L1 expression is still mandatory, as treatment with single anti-PD1 agent remains the standard of care in the subgroup of tumors with high PD-L1 expression.

Finding the best place of ICI combination with or without chemotherapy in the therapeutic strategy of advanced NSCLC and defining the subgroup that obtains the maximum benefit from this combination without compromising safety and economic impact remain the future challenges that might be answered in the near future for nivolumab plus ipilimumab.

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Footnote

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Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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