Letter to the Editor

Dual immune checkpoint blockade for non-small cell lung cancer patients with PD-L1 high expression: calling an end?

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We read with interest the KEYNOTE-598 trial (1), which did not meet its primary endpoints and was terminated early. Additional ipilimumab failed to amplify the efficacy of pembrolizumab in the 'tumor proportion score (TPS) high' population which could be attributed to several reasons.

First, the clinical role of ipilimumab in addition to PD-1 antibody in the first line treatment for non-small cell lung cancer (NSCLC) is marginal, as previously demonstrated by CheckMate 227 part 1 (2). However, discernment of whether combining an immune checkpoint inhibitor (ICI) with chemotherapy is more efficient than ICI monotherapy in a PD-L1 high population is of great importance. Evidence from a meta-analysis showed that although objective response rate (ORR) as well as progression-free survival (PFS) were improved in the combination group, the overall survival (OS) benefit presented was identical (3). While an anti-PD-1 antibody plus chemotherapy performs better than an anti-PD-L1 antibody plus chemotherapy for first line NSCLC regardless of PD-L1 expression (4), the difference of anti-PD-1 versus anti-PD-L1 monotherapy in a PD-L1 high expression population is not significant, with results from TC3/IC3 of IMpower-110 for OS hazard ratio (HR) 0.59 [95% confidence interval (CI): 0.40 to 0.89] (5) and EMPOWER-Lung 1 showing an OS HR of 0.57 (95% CI: 0.42 to 0.77) (6). Although cross-trial comparisons are fraught with difficulties, we do have similar numerical median survival data of ICI monotherapy for this population. Hence, with similar PFS and OS results of the KEYNOTE-024 and KEYNOTE-598 trials, pembrolizumab monotherapy would remain the standard of care for the first line setting of PD-L1 high expressors at the current stage.

Second, the toxicity profile of ipilimumab impacts the adverse event profile of dual ICI blockade. Adding ipilimumab was associated with a higher rate of grade 3–5 adverse events for NSCLC patients in KEYNOTE-598. With prior experience using ipilimumab in NSCLC, KEYNOTE-598 contributed evidence to the role of anti-CTLA-4 into the first line treatment of NSCLC. According to data from the use of durvalumab plus tremelimumab in the MYSTIC trial (7), the toxicity of CTLA-4 inhibitors is not restricted to ipilimumab. In balancing the survival benefit and toxicity risk of PD-L1 high expressors, dual ICI blockade of PD-L1/CTLA-4 might not be an optimal choice. Toxicity profile of ipilimumab could be reduced with lower dose or longer interval of treatment, indicating the dedicate balance of efficacy versus toxicity of anti-CTLA-4 antibody.

Third, the underlying biologic mechanisms might explain the failure of KEYNOTE-598. The PD-1/PD-L1 pathway is a major immune-related mechanism in these cancers, but the tumor immune microenvironment

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of patients with NSCLC with high PD-L1 expression may be 'inflammatory'. Thus, up-stream blockage of CTLA-4 may not bring additional benefits for this population. Retrospective studies of NSCLC with very-high PD-L1 expression levels (defined as 90% and above) have suggested PD-1 inhibitor monotherapy treatment rather than in combination with chemotherapy (8). Therefore, stratification measures might ensure randomized groups are evenly balanced by various PD-L1 levels in KEYNOTE-598. In KEYNOTE-598, PD-L1 expression >90% *vs.* 50–90% is not stratified, therefore there was no information regarding survival of these groups. The expression levels of PD-L1 remain the most common predictive biomarkers of the clinical benefits from PD-L1 inhibitors in the real world; although, whether high PD-L1 expression would predict clinical efficacy of PD-L1/CTLA-4 dual blockade is not known.

Finally, which is the optimal treatment strategy for NSCLC patients of high PD-L1 expression? Monotherapy of PD-L1 inhibitors works well for PD-L1 high expressors, however, it would be ideal to further prolong the median OS of 26.3 months that was achieved with pembrolizumab monotherapy, as reported in KEYNOTE-024 (9). The KEYNOTE-598 trial did not answer the question of whether adding chemotherapy to immunotherapy for PD-L1 high expressors would lead to further survival benefit. The ongoing trials of INSIGNA (NCT03793179) and PERSEE (NCT04547504) will provide further clarity.

The question remains whether there is any role for other dual checkpoint blockade other than CTLA-4 in NSCLC patients with high PD-L1 expression. The phase 2 trial CITYSCAPE analyzed an anti-TIGIT (T cell immunoreceptor with immunoglobulin and ITIM domain) antibody plus atezolizumab as a dual checkpoint blockade combination (10). Therein, PD-L1 high expressors appeared to benefit from adding anti-TIGIT antibody with an OS HR of 0.30 (95% CI: 0.15 to 0.61) in this subgroup, while patients with PD-L1 expression of 1–49% did not benefit from this combination, indicating a potential role of TIGIT for PD-L1 high expression NSCLC patients. The phase III SKYSCRAPER-01 trial (NCT04294810) will help to elucidate these results.

In conclusion, although not practice changing, the failure of KEYNOTE-598 provides insights for the current landscape of NSCLC treatment. Caution should be exercised when creating future designs for dual immunotherapy oncology clinical trials without promising results from exploratory phase II trials.

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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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