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LUNG CANCER

Frontline nivolumab — CheckMate 026 ends in stalemate

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The anti-PD-1 antibody nivolumab is an approved second-line therapy for advanced-stage non-small-cell lung cancer (NSCLC), but earlier use of this immunotherapeutic agent might be beneficial. In the phase III CheckMate 026 trial, David Carbone *et al*. addressed this question.

The researchers randomly assigned 541 patients with NSCLC and ≥1% PD-L1-positive tumour cells to receive frontline nivolumab or platinum-based chemotherapy. The primary analysis involved 428 patients with ≥5% PD-L1 positivity, and revealed, strikingly, that nivolumab did not improve progression-free survival (PFS) or overall survival (OS): median of 4.2 months and 14.4 months, respectively, versus 5.9 months and 13.2 months with chemotherapy. Similar results were reported for the entire trial population and, intriguingly, for the subgroup with a high level of (≥50%) PD-L1 positivity.

In an exploratory analysis, patients with a high tumoural mutation burden had a better response rate and longer PFS with nivolumab than with chemotherapy. Notably, 75% of patients with both a high mutation burden and high PD-L1 expression responded to nivolumab, compared with 32–34% of those with only one of these factors. OS between the treatment arms did not differ by mutation burden; however, 68% of the chemotherapy-treated patients received — and would be expected to respond well to — second-line nivolumab, which might at least partially explain this finding.

Indeed, the high rate of crossover and important imbalances favouring the chemotherapy arm, particularly the inclusion of greater numbers of patients with high PD-L1 expression and/or a high mutation burden, were highlighted as limitations of the data. "I think the biggest lessons from this trial are the importance of patient selection in optimizing the benefit from any modern therapy, and the role of chance, even in large phase III trials," Carbone opines.

He elaborates: "Until we have a really good biomarker, or biomarker panel to select patients, I think we will see surprisingly variable outcomes from immunotherapy trials. Prospective testing of tumour mutation burden is a start, but one should keep in mind that not all mutations are equivalent; algorithms are being developed to enumerate 'quality' neoantigens, which may be a better approach. Moreover, high numbers of mutations might also increase the chance of mutations disrupting the antigen-presentation pathway, which has not been taken into account in any modern study."

The quest for robust predictors of responsiveness to immunotherapy has only just begun. Moreover, the role of PD-1 blockade in the frontline treatment of NSCLC requires clarification: outside of a select few patients, is prior or concurrent chemotherapy needed to sensitize tumours to immunotherapy?

David Killock

ORIGINAL ARTICLE Carbone, D. P. *et al.* First-line nivolumab in stage IV or recurrent non-small-cell lung cancer. *N. Engl. J. Med.* **376**, 2415–2426 (2017)