> chemotherapy alone is no longer the standard of care for patients with metastatic NSCLC

and estimated 12-month overall survival (69.2% versus 49.4%; $P<0.001$) relative to those in the placebo group. The risk of grade ≥3 adverse events was similar among patients in both groups (67.2% versus 65.8%). Immune-mediated adverse events were reported separately, with events of any grade occurring more frequently in the pembrolizumab group (in 22.7% versus 11.9%).

These findings confirm the superiority of pembrolizumab plus chemotherapy over chemotherapy alone as a first-line treatment for patients with treatment-naive metastatic NSCLC, irrespective of PD-L1 expression. "This study and CheckMate 227 (among others) suggest that chemotherapy alone is no longer the standard of care for patients with metastatic NSCLC and that immunotherapy is the common backbone on which we will build future combination therapy," Gandhi concludes.

Peter Sidaway

ORIGINAL ARTICLE Gandhi, L. et al. Pembrolizumab plus chemotherapy in metastatic non-small-cell lung cancer. *N. Engl. J. Med.* https://doi.org/10.1056/NEJMoa1801005 (2018)

> we are now evaluating the subset of T cells responsible for the therapeutic effect

Melenhorst summarizes these findings: "we have identified an early memory CD8$^+$ T cell population in pre-manufacturing T cells (that is, before cell culture and gene transfer), the frequency of which predicts response to CTL019 therapy in patients with CLL, confirming that the intrinsic quality of T cells is the driver of therapeutic success."

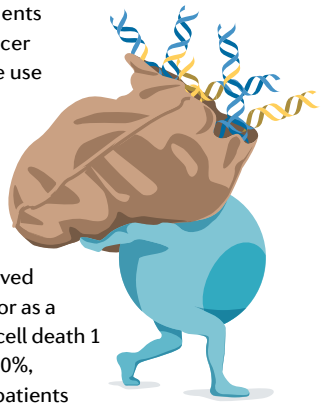
The CAR T cell manufacturing process can be improved accordingly: "we are now evaluating the subset of T cells responsible for the therapeutic effect and removing the other populations," states Melenhorst, who is also interested in characterizing patient-derived T cell populations associated with a favourable response to CAR T cell therapy in other malignancies.

Diana Romero

ORIGINAL ARTICLE Fraietta, J. A. et al. Determinants of response and resistance to CD19 chimeric antigen receptor (CAR) T cell therapy of chronic lymphocytic leukemia. *Nat. Med.* **24**, 563–571 (2018)

IMMUNOTHERAPY

Nivolumab–ipilimumab — exploiting the mutation burden of NSCLCs



Credit: S. Bradbrook/Macmillan Publishers Limited

Benefit from frontline immunotherapy in patients with advanced-stage non-small-cell lung cancer (NSCLC) seems to depend on the appropriate use of biomarkers or drug combinations. Now, Matthew Hellmann of the Memorial Sloan Kettering Cancer Center and colleagues extend these observations to combination immunotherapy with nivolumab and ipilimumab (nivo + ipi).

Whereas first-line pembrolizumab is approved in combination with standard chemotherapy, or as a monotherapy in patients with a programmed cell death 1 ligand 1 (PD-L1) tumour proportional score ≥50%, frontline nivolumab was not found to benefit patients with ≥5% tumoural PD-L1 expression. In the ongoing phase III CheckMate 227 trial, two hypotheses are being tested: first, that nivo + ipi is efficacious in this setting, as suggested by results of the phase I CheckMate 012 study; second, that tumour mutation burden (TMB) is a useful predictive biomarker of a response to this combination, as indicated by data from the phase II CheckMate 568 study.

In CheckMate 227, patients with chemotherapy-naive, stage IV or recurrent NSCLC with ≥1% PD-L1 expression were randomly assigned to receive nivo + ipi, nivolumab alone, or standard chemotherapy, whereas those with <1% PD-L1 received nivo + ipi, nivolumab plus chemotherapy, or chemotherapy alone. TMB was also evaluated, and data now published in the *New England Journal of Medicine* are focused on patients with a high TMB (≥10 mutations per Mb).

In the high-TMB group, nivo + ipi improved 1-year progression-free survival (PFS) compared with chemotherapy: 43% versus 13% (HR 0.58, 95% CI 0.41–0.81; $P<0.001$). Notably, PFS was similar with nivo + ipi versus chemotherapy in those with a low TMB (HR 1.07, 95% CI 0.84–1.35), demonstrating the utility of the TMB biomarker and cut-point. Importantly, benefit for the high-TMB group was independent of PD-L1 expression or histology (squamous versus nonsquamous). Interestingly, nivolumab monotherapy was less beneficial in those with a high TMB (1-year PFS 29% versus 42% for nivo + ipi, and 16% with chemotherapy).

"This study establishes nivo + ipi as a frontline treatment option for patients with TMB-high NSCLC," Hellmann opines, adding "the clinical benefit of nivo + ipi was substantial, deep, and durable, and this approach spares the use of chemotherapy in the first-line setting."

"These results confirm our finding from CheckMate 012, recently published in *Cancer Cell*, that a high TMB is a strong and independent biomarker for predicting benefit with combination immunotherapy," states Hellmann. Unfortunately, the data from this analysis indicate that even combination immunotherapy cannot overcome the hurdle of a low TMB.

"TMB can be assessed using genetic profiling panels that are already routine in many clinical practices and simultaneously provide information to guide the use of molecularly targeted therapies; overall, TMB builds on the progress made in precision medicine and broadens the actionability of routine profiling of NSCLCs," Hellmann concludes.

David Killock

ORIGINAL ARTICLES Hellmann, M. D. et al. Nivolumab plus ipilimumab in lung cancer with a high tumor mutational burden. *N. Engl. J. Med.* https://doi.org/10.1056/NEJMoa1801946 (2018) | Hellmann, M. D. et al. Genomic features of response to combination immunotherapy in patients with advanced non-small-cell lung cancer. *Cancer Cell.* https://doi.org/10.1016/j.ccell.2018.03.018 (2018)