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LUNG CANCER

Anti-PD-1 therapy in the frontline

Successes with the anti-PD-1 antibodies pembrolizumab and nivolumab in the second-line treatment of advanced-stage non-small-cell lung cancer (NSCLC) have inevitably led to trials in the first-line setting. Results from three such trials were presented to packed crowds at the ESMO 2016 Congress.

In the phase III KEYNOTE-024 trial, pembrolizumab monotherapy was compared with platinum-based doublet chemotherapy in 305 treatment-naive patients with PD-L1 expression on ≥50% of tumour cells. This biomarker threshold has been shown to enrich for responders to pembrolizumab; however, only ~30% of the patients tested expressed PD-L1 at this high level. Results of this trial, also published in the *New England Journal of Medicine*, reveal an unprecedented objective response rate (ORR) of 45% with pembrolizumab (versus 28% with chemotherapy), and improved progression-free survival (PFS) versus that of the chemotherapy group (HR 0.50, P <0.001); overall survival (OS) was also prolonged in the immunotherapy group (HR 0.60, P = 0.005), despite crossover being permitted. "The significant improvement in PFS and OS is very relevant given that platinum-based chemotherapy has, for decades, been the mainstay therapy for treatment-naive patients without *EGFR* or *ALK* aberrations," explains lead author Martin Reck.

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S. Bradbrook/NPG

Toxicities were less common and less severe in the immunotherapy arm than in the chemotherapy arm; immune-related adverse events occurred more often with immunotherapy, but were mostly manageable.

"These data will change the way in which patients with NSCLC are evaluated and treated: we believe that the data support upfront testing of all untreated patients for PD-L1 expression, and that this information should be used to design the most-appropriate therapeutic plan," Reck opines. "The opportunity of a more-efficacious and better-tolerated first-line treatment option represents a practice-changing perspective for patients with NSCLC and a high degree of PD-L1 positivity."

Reck adds, "we are very interested in determining whether patients with lesser degrees of PD-L1 expression can benefit from pembrolizumab, and whether combinations can improve on the efficacy observed." However, these issues have already been addressed, to some extent, in the two other trials presented.

In the CheckMate 026 trial, investigators compared nivolumab and first-line platinum-based chemotherapy in 541 patients with PD-L1 expression on ≥1% of tumour cells. Interestingly, the results in 423 patients with ≥5% PD-L1 positivity were negative in terms of both PFS (HR 1.15) and OS (HR 1.02). These findings suggest that patients with higher PD-L1 positivity are more likely to derive benefit from anti-PD-1 therapy, but differences in the baseline characteristics of the KEYNOTE and CheckMate trial populations necessitate confirmation of the role of PD-L1 as a biomarker in the frontline setting.

Finally, the addition of pembrolizumab to first-line carboplatin and pemetrexed chemotherapy was investigated in expansion cohort G of the phase II KEYNOTE-021 trial. The results, now published in *The Lancet Oncology*, are impressive. The ORR in the immunotherapy arm was 55% (trumping that seen even in KEYNOTE-024) versus 29% in the chemotherapy-only arm. Patients were enrolled independently of PD-L1 positivity, but those with PD-L1 on ≥50% of tumour cells had an ORR of 80%. PFS was improved with pembrolizumab (HR 0.53, P = 0.01); notably, the PFS curves separated very early, suggesting that the majority of patients benefitted from immune-checkpoint inhibition, rather than a minority as is typically seen. Moreover, toxicity of the combination regimen was, in general, only modestly increased compared with that of chemotherapy alone.

These results are exciting, and approval of pembrolizumab in the frontline setting must surely be expected soon. However, whether a particular approach — monotherapy or combination treatment — is superior remains to be determined.

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ORIGINAL ARTICLES Reck, M. *et al.* Pembrolizumab versus chemotherapy for PD-L1-positive non-small-cell lung cancer. *N. Engl. J. Med.* http://dx.doi.org/10.1056/NEJMoa1606774 (2016) | Langer, C. J. *et al.* Carboplatin and pemetrexed with or without pembrolizumab for advanced, non-squamous non-small-cell lung cancer: a randomised, phase 2 cohort of the open-label KEYNOTE-021 study. *Lancet Oncol.* http://dx.doi.org/10.1016/S1470-2045(16)30498-3 (2016) | Socinski, M. A. *et al.* CheckMate 026: a phase 3 trial of nivolumab vs investigator's choice (IC) of platinum-based doublet chemotherapy (PT-DC) as first-line therapy for stage IV/recurrent programmed death ligand 1 (PD-L1)-positive NSCLC. Abstr. LBA7_PR presented at the ESMO 2016 Congress