Editorial Commentary

Pembrolizumab monotherapy for PD-L1 ≥50% non-small cell lung cancer, undisputed first choice?

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The recent introduction of immunotherapy has drastically changed the treatment landscape of patients with advanced non-small cell lung cancer (NSCLC). Approval by the US Food and Drug Administration and the European Medicines Agency of immune checkpoint inhibitors (ICIs) soon followed after several phase III trials showed superior overall survival (OS) of the monoclonal antibody therapy directed against the PD-1 receptor (nivolumab and pembrolizumab) and its ligand PD-L1 (atezolizumab) over previously standard of care (SoC) docetaxel (1-5). In first-line setting, the randomized phase III KEYNOTE-024 trial was the first study to show an OS benefit of pembrolizumab over platinum-doublet chemotherapy in treatment-naïve patients with metastatic NSCLC harbouring a PD-L1 tumor proportion score (TPS) of ≥50% (HR 0.60; 95% CI, 0.41–0.89; P=0.005) (6). At the second interim analysis the primary endpoint—progression free survival (PFS)—was reached and the trial was prematurely stopped. This resulted in approval for first-line treatment with pembrolizumab for advanced NSCLC with a TPS of ≥50%.

In the *Journal of Clinical Oncology*, Reck and colleagues now report the updated results of KEYNOTE-024, allowing further insights in the advantages of choosing pembrolizumab monotherapy over platinum-based chemotherapy, also by taking into account crossover effects (7). As mentioned, 305 treatment-naïve patients with metastatic NSCLC with a PD-L1 TPS ≥50% and *EGFR/ALK* negative status, were randomly assigned to receive either pembrolizumab (n=154) or platinum-based chemotherapy (n=151). Besides updated efficacy and safety outcomes, several adjusted analyses were performed among patients who crossed over from chemotherapy to pembrolizumab per protocol. Improvement of median OS was still in favor of the pembrolizumab treatment: 30.0 months (95% CI, 18.3–NA) *vs.* 14.2 months (95% CI, 9.8–19.0 months) in the chemotherapy arm (HR 0.63; 95% CI, 0.47–0.86; P=0.002). When adjusted for crossover the HR was 0.49 (95% CI, 0.34–0.69) in favor of pembrolizumab. Toxicity data in the crossover group during pembrolizumab was similar to first-line pembrolizumab. The authors conclude that these results support pembrolizumab monotherapy as a SoC regimen for first-line treatment of advanced NSCLC with PD-L1 TPS ≥50% and without *EGFR/ALK* alterations.

Although these results do seem convincing, the final conclusion by the authors has to be reviewed with caution. A previous trial, Checkmate-026, comparing nivolumab to platinum-doublet chemotherapy in first-line setting failed to reach its primary endpoint (8). The primary endpoint was PFS in patients with PD-L1 expression ≥5%, so it has to be taken into account that this cohort was enriched with patients with a lesser change of benefit on immunotherapy. However, in an OS subgroup analyses, PD-L1 ≥50% patients did not reach a significant improvement with

nivolumab over chemotherapy. Differences in study design, choice of PD-1 antibody and PD-L1 analyses can explain some of the discordances between these two studies and although subgroup analyses have to be treated with caution, it seems relevant to realize that the use of different PD-L1 protocols in everyday clinical setting may impact patient outcomes.

A subsequent study, KEYNOTE-042, investigated pembrolizumab *vs.* platinum-based chemotherapy in first-line for patients with PD-L1 TPS ≥1% (9). Although the PD-L1 TPS ≥50% subgroup within this study showed an OS benefit in favor of pembrolizumab, it was numerically lower compared to KEYNOTE-024. Also, no significant PFS benefit was reached and in the first 6 months of treatment patients in the chemotherapy group even seemed to perform better as indicated by the crossing of the PFS and OS curves at that time point. The reason for this was sought in a more heterogeneous study population.

Recently, findings from the randomized phase III trials KEYNOTE-189 and KEYNOTE-407 showed that pembrolizumab in combination with platinum-based chemotherapy in first-line significantly prolonged PFS and OS compared to chemotherapy alone in patients with metastatic non-squamous and squamous NSCLC, irrespective of PD-L1 TPS (10,11). No increase in toxicity was observed by adding pembrolizumab. The benefit in PFS and OS increased for higher PD-L1 expressing subgroups. This 'triple therapy' approach has now entered its way into the clinic.

In another first-line study, IMpower 150, patients with non-squamous NSCLC irrespective of PD-L1 expression were randomized between carboplatin, paclitaxel and bevacizumab (BCP) *vs.* carboplatin, paclitaxel and atezolizumab (ACP) *vs.* all 4 agents (ABCP) (12). It met its co-primary endpoint of PFS and OS for ABCP *vs.* BCP. Although excluded for the primary endpoint, patients with *EGFR/ALK* alterations were allowed to participate and showed improved PFS by the addition of atezolizumab, making this an attractive possibility for applying ICIs in this normally immunotherapy-unresponsive subgroup.

In KEYNOTE-024, the majority of the patients in the chemotherapy arm crossed over to second-line pembrolizumab (65.1%), which was close to the expected percentage of 70%. Overall response rate (ORR) on pembrolizumab in the crossover group was less than half compared to first-line: 20.7% *vs.* 44.8% (6,7). This ORR was also lower to that of patients with PD-L1 TPS ≥50% in the KEYNOTE-010 comparing two dosages of pembrolizumab to docetaxel in second-line setting, which was around 30% (2). Although, the lower response rate in the crossover group 'inflated' KEYNOTE-024 results, it further strengthens the conclusion that patients with NSCLC with a PD-L1 TPS ≥50% are better off with pembrolizumab in first-line setting. But does the conclusion of pembrolizumab *monotherapy* being the optimal choice for all PD-L1 TPS ≥50% patients hold up?

How to bring into perspective the crossing of the curves at 6 months in KEYNOTE-042 and the negative Checkmate-026 study? Unfortunately, we still lack a trial comparing 'triple therapy' to pembrolizumab monotherapy in NSCLC with high PD-L1 expression. In KEYNOTE-042, some patients with NSCLC with PD-L1 expression of ≥50% still seem to benefit from first-line chemotherapy, questioning whether PD-L1 expression is the best biomarker for making this choice. Tumor mutational burden (TMB) may be a promising marker—by itself or in addition to PD-L1 expression—to select patients where chemotherapy can be omitted in the first-line regime, as suggested by additional analysis in the Checkmate-026 study. Unfortunately, TMB testing is still not readily available in the clinic. Also, single-agent immunotherapy has been described of being able to elicit hyperprogression of disease and the addition of chemotherapy might prevent this not yet well understood but detrimental phenomenon (13).

We do agree with the authors that pembrolizumab should be offered to all patients that present with advanced NSCLC and a PD-L1 TPS ≥50%, but we also believe that it is too early to withhold chemotherapy unless after clear consultation with the patient.

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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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