JOSHA`s CRITICAL REVIEW OF „Pembrolizumab plus Chemotherapy in Metastatic Non–Small-Cell Lung Cancer”

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JOSHA`s CRITICAL REVIEW OF „PEMBROLIZUMAB PLUS CHEMOTHERAPY IN METASTATIC NON–SMALL-CELL LUNG CANCER".

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In this double-blind, phase 3 trial, 616 patients with metastatic nonsquamous NSCLC without sensitizing EGFR or ALK mutations were randomly assigned to receive pemetrexed and a platinum-based drug plus either 200 mg of pembrolizumab, a monoclonal antibody against programmed death (PD-1), or placebo every 3 weeks for 4 cycles, followed by up to a total of 35 cycles of either combination as maintenance therapy. After a median follow-up of 10.5 months, the estimated rate of overall survival at 12 months was 69.2% in the pembrolizumab-combination group versus 49.4% in the placebo combination group (P<0.001). Median progression-free survival was 8.8 months (95% CI, 7.6 to 9.2) in the pembrolizumab-combination group and 4.9 months in the placebo-combination group (P<0.001). Adverse events of grade 3 or higher occurred in 67.2% of the patients in the pembrolizumab-combination group and in 65.8% of those in the placebo-combination group.

JOSHA`s Conclusion: SIGNIFICANT PROGRESS WITHOUT ADDITIONAL GRADE 3 TOXICITY

A striking benefit in overall survival was observed, and a less striking benefit in progression-free survival. This is quite in contrast to other recent studies with checkpoint inhibitors demonstrating a significant event-free survival benefit but did not demonstrate an overall survival benefit – as yet. Perhaps disease control without added toxicity is a better strategy than trying to eradicate the last cancer cells with added treatment toxicity? The innovative therapeutic strategies based on concepts of clonal evolution proposed by Cassandra Willyard (Cancer: An evolving threat, Nature 532, 166, 2016) could be of relevance here. Also, the role of type and duration of maintenance therapy should be studied further.

PD-1 blockers are approved for several different types of malignancies. It is assumed that their efficacy is based on an accrual of CD8-psitive T cells into the tumors with suitable immune gene patterns and the interaction of tumor cells with T cells and antigen-presenting cells. In this context it is interesting to note that adjuvant 200 mg pembrolizumab every 3 weeks for up to 1 year resulted in significantly longer recurrence-free survival than placebo in a phase III trial with >1000 patients who had resected cutaneous melanoma with metastasis to regional lymph nodes, regardless of PD-1 ligand expression of melanoma-positive lymph nodes at enrollment. New toxicities were not observed. About 15 % of the pembrolizumab-treated patients experienced grade 3 to 5 toxicities during the 1-year-treatment, which seems to be meaningfully less toxic than the profile of the pricey anti-CTL4 antibody ipilimumab. The trial (EORTC 1325) is planned to continue to its secondary endpoints, including overall survival (A.M.M.Eggermont et al, N Engl J Med 2018;378:1789-801. DOI: 10.1056/NEJMoa1802357).

Original Article

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Original Abstract

Background First-line therapy for advanced non–small-cell lung cancer (NSCLC) that lacks targetable mutations is platinum-based chemotherapy. Among patients with a tumor proportion score for programmed death ligand 1 (PD-L1) of 50% or greater, pembrolizumab has replaced cytotoxic chemotherapy as the first-line treatment of choice. The addition of pembrolizumab to chemotherapy resulted in significantly higher rates of response and longer progression-free survival than chemotherapy alone in a phase 2 trial.

Methods In this double-blind, phase 3 trial, we randomly assigned (in a 2:1 ratio) 616 patients with metastatic nonsquamous NSCLC without sensitizing EGFR or ALK mutations who had received no previous treatment for metastatic disease to receive pemetrexed and a platinum-based drug plus either 200 mg of pembrolizumab or placebo every 3 weeks for 4 cycles, followed by pembrolizumab or placebo for up to a total of 35 cycles plus pemetrexed maintenance therapy. Crossover to pembrolizumab monotherapy was permitted among the patients in the placebo-combination group who had verified disease progression. The primary end points were overall survival and progression-free survival, as assessed by blinded, independent central radiologic review**.**

Results After a median follow-up of 10.5 months, the estimated rate of overall survival at 12 months was 69.2% (95% confidence interval [CI], 64.1 to 73.8) in the pembrolizumab-combination group versus 49.4% (95% CI, 42.1 to 56.2) in the placebocombination group (hazard ratio for death, 0.49; 95% CI, 0.38 to 0.64; P<0.001). Improvement in overall survival was seen across all PD-L1 categories that were evaluated. Median progression-free survival was 8.8 months (95% CI, 7.6 to 9.2) in the pembrolizumab-combination group and 4.9 months (95% CI, 4.7 to 5.5) in the placebo-combination group (hazard ratio for disease progression or death, 0.52; 95% CI, 0.43 to 0.64; P<0.001). Adverse events of grade 3 or higher occurred in 67.2% of the patients in the pembrolizumab-combination group and in 65.8% of those in the placebo-combination group.

Conclusions

In patients with previously untreated metastatic nonsquamous NSCLC without EGFR or ALK mutations, the addition of pembrolizumab to standard chemotherapy of pemetrexed and a platinum-based drug resulted in significantly longer overall survival and progression-free survival than chemotherapy alone. (Funded by Merck; KEYNOTE-189 ClinicalTrials.gov number, NCT02578680.)

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