Domanda estratta n. 4

DOMANDE COLLOQUIO

1) Che cosa è un criterio di stratificazione in uno studio di fase III?

2) Che cosa è la randomizzazione in uno studio di fase III?

3) Che cosa è un fattore predittivo in oncologia?

4) Che cosa è un fattore prognostico in oncologia?

Domanda estratta n. 4

DOMANDE PROVA INFORMATICA

1) Che cos'è un database?

2) A cosa serve Power Point?

3) A cosa serve Word?

4) Che cos'è Excel?

Domanda estratta n. 4

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Pembrolizumab versus Chemotherapy for PD-L1–Positive Non–Small-Cell Lung Cancer

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ABSTRACT

BACKGROUND

Pembrolizumab is a humanized monoclonal antibody against programmed death 1 (PD-1) that has antitumor activity in advanced non–small-cell lung cancer (NSCLC), with increased activity in tumors that express programmed death ligand 1 (PD-L1).

METHODS

In this open-label, phase 3 trial, we randomly assigned 305 patients who had previously untreated advanced NSCLC with PD-L1 expression on at least 50% of tumor cells and no sensitizing mutation of the epidermal growth factor receptor gene or translocation of the anaplastic lymphoma kinase gene to receive either pembrolizumab (at a fixed dose of 200 mg every 3 weeks) or the investigator's choice of platinum-based chemotherapy. Crossover from the chemotherapy group to the pembrolizumab group was permitted in the event of disease progression. The primary end point, progression-free survival, was assessed by means of blinded, independent, central radiologic review. Secondary end points were overall survival, objective response rate, and safety.

RESULTS

Median progression-free survival was 10.3 months (95% confidence interval [CI], 6.7 to not reached) in the pembrolizumab group versus 6.0 months (95% CI, 4.2 to 6.2) in the chemotherapy group (hazard ratio for disease progression or death, 0.50; 95% CI, 0.37 to 0.68; P<0.001). The estimated rate of overall survival at 6 months was 80.2% in the pembrolizumab group versus 72.4% in the chemotherapy group (hazard ratio for death, 0.60; 95% CI, 0.41 to 0.89; P=0.005). The response rate was higher in the pembrolizumab group than in the chemotherapy group (44.8% vs. 27.8%), the median duration of response was longer (not reached [range, 1.9+ to 14.5+ months] vs. 6.3 months [range, 2.1+ to 12.6+]), and treatment-related adverse events of any grade were less frequent (occurring in 73.4% vs. 90.0% of patients), as were grade 3, 4, or 5 treatment-related adverse events (26.6% vs. 53.3%).

CONCLUSIONS

In patients with advanced NSCLC and PD-L1 expression on at least 50% of tumor cells, pembrolizumab was associated with significantly longer progression-free and overall survival and with fewer adverse events than was platinum-based chemotherapy. (Funded by Merck; KEYNOTE-024 ClinicalTrials.gov number, NCT02142738.)

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*A complete list of investigators in the KEYNOTE-024 trial is provided in the Supplementary Appendix, available at NEJM.org.

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Approximately 23 to 28% of patients with advanced non–small-cell lung cancer (NSCLC) have a high level of programmed death ligand 1 (PD-L1) expression, which is defined as membranous PD-L1 expression on at least 50% of tumor cells, regardless of the staining intensity (i.e., a PD-L1 tumor proportion score of 50% or greater).[1,2] Data from the phase 1 KEYNOTE-001 and phase 3 KEYNOTE-010 studies indicated that patients with advanced NSCLC and a PD-L1 tumor proportion score of 50% or greater were more likely than those with lower tumor proportion scores to have a response to pembrolizumab, a highly selective, humanized monoclonal antibody against programmed death 1 (PD-1) that prevents PD-1 from engaging PD-L1 and PD-L2.[1-3]

Current first-line treatment decisions for advanced NSCLC are based on the presence of genetic aberrations, such as sensitizing mutations of epidermal growth factor receptor (*EGFR*) and translocations of anaplastic lymphoma kinase (*ALK*). However, most patients with NSCLC do not harbor these oncogenic drivers, and for these patients, treatment options are limited to cytotoxic chemotherapy. In patients enrolled in the KEYNOTE-001 trial who had previously untreated NSCLC and a PD-L1 tumor proportion score of 50% or greater, pembrolizumab (administered every 2 or 3 weeks at a dose of 10 mg per kilogram of body weight) was associated with a response rate of 58.3%, median progression-free survival of 12.5 months, and 24-month overall survival of 60.6%.[4]

In the international, randomized, open-label, phase 3 KEYNOTE-024 trial, we compared pembrolizumab (administered at a fixed dose of 200 mg every 3 weeks) with the investigator's choice of cytotoxic chemotherapy as first-line therapy for patients with advanced NSCLC and a PD-L1 tumor proportion score of 50% or greater.

METHODS

PATIENTS

Patients 18 years of age or older were eligible for enrollment if they had histologically or cytologically confirmed stage IV NSCLC with no sensitizing *EGFR* mutations or *ALK* translocations, had undergone no previous systemic therapy for metastatic disease, and had an Eastern Cooperative Oncology Group (ECOG) performance-status score of 0 or 1 (on a 5-point scale, with 0 indicating no symptoms and higher scores indicating increasing disability), at least one measurable lesion according to Response Evaluation Criteria in Solid Tumors (RECIST), version 1.1,[5] a life expectancy of at least 3 months, and a PD-L1 tumor proportion score of 50% or greater. Patients were ineligible if they were receiving systemic glucocorticoids (excluding daily glucocorticoid-replacement therapy for conditions such as adrenal or pituitary insufficiency) or other immunosuppressive treatment or if they had untreated brain metastases, active autoimmune disease for which they had received systemic treatment during the previous 2 years, active interstitial lung disease, or a history of pneumonitis for which they had received glucocorticoids.

TRIAL DESIGN AND TREATMENT

Patients were randomly assigned, in a 1:1 ratio, to receive treatment with either pembrolizumab (administered intravenously at a dose of 200 mg every 3 weeks) for 35 cycles or the investigator's choice of one of the following five platinum-based chemotherapy regimens for 4 to 6 cycles: carboplatin plus pemetrexed, cisplatin plus pemetrexed, carboplatin plus gemcitabine, cisplatin plus gemcitabine, or carboplatin plus paclitaxel (Table S1 in the Supplementary Appendix, available with the full text of this article at NEJM.org). Chemotherapy regimens that included pemetrexed were permitted only for patients who had nonsquamous tumors; these patients could continue to receive pemetrexed as maintenance therapy after the completion of combination chemotherapy. The intended chemotherapy regimen, including the use of pemetrexed maintenance therapy, was chosen before the patient underwent randomization. Randomization was stratified by ECOG performance-status score (0 vs. 1), tumor histologic type (squamous vs. nonsquamous), and region of enrollment (East Asia vs. non–East Asia) and did not include any provisions regarding equal distribution of enrollment across participating sites or stratification by site. Treatment was continued for the specified number of cycles or until the patient had radiologic disease progression (defined according to RECIST; Table S2 in the Supplementary Appendix), had treatment-related adverse events of unacceptable severity, or withdrew consent or until the investigator decided to withdraw the patient, whichever occurred first. Patients in the chemotherapy group who had disease progression, which was verified

by means of blinded, independent, central radiologic review, could cross over to receive pembrolizumab, if safety criteria were met. There was no preplanned crossover from the pembrolizumab group to the chemotherapy group, and there were no guidelines regarding therapy after disease progression for patients in the pembrolizumab group. Patients in either treatment group who were in clinically stable condition and were considered by the investigator to be deriving clinical benefit could continue therapy after disease progression. Full guidance on treatment decisions, including the management of adverse events, can be found in the trial protocol, available at NEJM.org.

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TRIAL ASSESSMENTS

PD-L1 expression was assessed in formalin-fixed tumor samples at a central laboratory with the use of the commercially available PD-L1 IHC 22C3 pharmDx assay (Dako North America).[6,7] Tumor samples were obtained by core-needle or excisional biopsy or from tissue resected at the time the metastatic disease was diagnosed. Fine-needle aspirates or samples obtained from irradiated sites or before the administration of adjuvant or neoadjuvant therapy were not permitted to be used. Imaging studies of the tumors were obtained every 9 weeks, and the response to treatment was assessed according to RECIST by means of blinded, independent, central radiologic review. Adverse events were reviewed, a physical examination was performed, and vital signs, a complete blood count with a differential count, and a comprehensive blood panel were assessed every 3 weeks during treatment and at the time of treatment discontinuation; T3, free T4, and thyrotropin were assessed every 6 weeks. During the survival follow-up phase, patients were contacted every 2 months for an assessment of survival. The full assessment schedule is available in the trial protocol. All adverse events and abnormalities were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.0.

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END POINTS

The primary end point was progression-free survival, which was defined as the time from randomization to disease progression or death from any cause. Secondary end points included overall survival, which was defined as the time from randomization to death from any cause; objective response rate, which was defined as the percentage of patients with a confirmed complete or partial response; and safety. An exploratory end point was duration of response, which was defined as the time from the first documentation of a complete or partial response to disease progression. A full list of end points is available in the protocol. Efficacy was assessed in the intention-to-treat population, which included all patients who underwent randomization. Safety was assessed in the as-treated population, which included all patients who received at least one dose of the assigned trial treatment.

TRIAL OVERSIGHT

The KEYNOTE-024 trial was designed by Merck representatives and academic advisors. Data were collected by investigators and associated site personnel, analyzed by statisticians employed by Merck, and interpreted by academic authors and Merck representatives. An external data and safety monitoring committee oversaw the trial and assessed the safety and efficacy at prespecified interim analyses. Committee members are listed in the Supplementary Appendix.

The trial protocol and all amendments were approved by the appropriate institutional review board or independent ethics committee at each trial center. The trial was conducted in accordance with Good Clinical Practice guidelines and the provisions of the Declaration of Helsinki. All the patients provided written informed consent before enrollment.

All the authors had full access to the data, vouch for the completeness and accuracy of the data, and attest that the trial was conducted in accordance with the protocol and all amendments. The first draft of the manuscript was written by the first and last authors with input from authors employed by Merck. All the authors participated in reviewing and editing the manuscript, and approved the submitted draft. As part of the site agreement signed before trial participation, investigators agreed to keep all aspects of the trial, including the resultant data, confidential.

STATISTICAL ANALYSIS

The Kaplan–Meier method was used to estimate progression-free and overall survival. For the analysis of progression-free survival, data for patients who were alive and had no disease progression or who were lost to follow-up were censored at the time of the last tumor assess-