Non-small-cell lung

Durvalumab plus tremelimumab alone or in combination with low-dose or hypofractionated radiotherapy in metastatic non-small-cell lung cancer refractory to previous PD(L)-1 therapy: an open-label, multicentre, randomised, phase II trial

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BACKGROUND

Patients with non-small-cell lung cancer (NSCLC) that are resistant to PD-1 and PD-L1 (PD[L]-1)-targeted therapy have poor outcomes. Studies suggest that radiotherapy could enhance antitumour immunity. Therefore, we investigated the potential benefit of PD-L1 (durvalumab) and CTLA-4 (tremelimumab) inhibition alone or combined with radiotherapy.

METHODS

This open-label, multicentre, randomised, phase II trial was done by the National Cancer Institute Experimental Therapeutics Clinical Trials Network at 18 US sites. Patients aged 18 years or older with metastatic NSCLC, an Eastern Cooperative Oncology Group performance status of 0.0 or 1.0, and progression during previous PD(L)-1 therapy were eligible. They were randomly assigned (1:1:1) in a web-based system by the study statistician using a permuted block scheme (block sizes of three or six) without stratification to receive either durvalumab (1500 mg intravenously every four weeks for a maximum of 13 cycles) plus tremelimumab (75 mg intravenously every four weeks for a maximum of four cycles) alone or with low-dose (0·5 Gy delivered twice per day, repeated for two days during each of the first four cycles of therapy) or hypofractionated radiotherapy (24 Gy total delivered over three 8.0-Gy fractions during the first cycle only), one week after initial durvalumab-tremelimumab administration. Study treatment was continued until one year or until progression. The primary endpoint was overall response rate (best locally assessed confirmed response of a partial or complete response) and, along with safety, was analysed in patients who received at least one dose of study therapy. The trial is registered withClinicalTrials.gov, NCT02888743, and is now complete.

FINDINGS

Between 24 Aug 2017, and 29 March 2019, 90 patients were enrolled and randomly assigned, of whom 78 (26 per group) were treated. This trial was stopped due to futility assessed in an interim analysis. At a median follow-up of 12·4 months (IQR 7·8-15·1), there were no differences in overall response rates between the durvalumab-tremelimumab alone group (three [11·5%, 90% CI 1·2-21·8] of 26 patients) and the low-dose radiotherapy group (two [7·7%, 0·0-16·3] of 26 patients; p=0·64) or the hypofractionated radiotherapy group (three [11·5%, 1·2-21·8] of 26 patients; p=0·99). The most common grade 3.0-4.0 adverse events were dyspnoea (two [8%] in the durvalumab-tremelimumab alone group; three [12%] in the low-dose radiotherapy group; and three [12%] in the hypofractionated radiotherapy group) and hyponatraemia (one [4.0%] in the durvalumab-tremelimumab alone group vs two [8.0%] in the low-dose radiotherapy group vs three [12%] in the hypofractionated radiotherapy group). Treatment-related serious adverse events occurred in one (4.0%) patient in the durvalumab-tremelimumab alone group (maculopapular rash), five (19%) patients in

the low-dose radiotherapy group (abdominal pain, diarrhoea, dyspnoea, hypokalemia, and respiratory failure), and four (15%) patients in the hypofractionated group (adrenal insufficiency, colitis, diarrhoea, and hyponatremia). In the low-dose radiotherapy group, there was one death from respiratory failure potentially related to study therapy.

INTERPRETATION

Radiotherapy did not increase responses to combined PD-L1 plus CTLA-4 inhibition in patients with NSCLC resistant to PD(L)-1 therapy. However, PD-L1 plus CTLA-4 therapy could be a treatment option for some patients. Future studies should refine predictive biomarkers in this setting.