Durvalumab improves progression-free survival in stage III lung cancer

September 11 2017

Durvalumab improves progression-free survival in patients with locally advanced, unresectable stage II lung cancer, according to late-breaking results from the phase III PACIFIC trial presented today at the ESMO 2017 Congress in Madrid and published in the *New England Journal of Medicine*.

About one-third of patients with non-small-cell lung cancer (NSCLC) have a stage III presentation. Standard treatment with platinum-based chemotherapy concurrent with radiation therapy gives a progression-free survival of about eight months and only 15% of patients are alive at five years.

PACIFIC is the first phase III trial to test an immune checkpoint inhibitor as sequential treatment in patients with stage III NSCLC who had not progressed following platinum-based chemotherapy concurrent with radiation therapy.

"There is evidence that synergy between radiotherapy and immunotherapy, such programmed death-ligand 1 (PD-L1) inhibitors, could increase the probability of response," said first author Dr Luis Paz-Ares, chair, Medical Oncology Department, Hospital Universitario Doce de Octubre, Madrid, Spain. "We therefore explored the impact of PD-L1 inhibition after standard chemoradiation treatment."

The PACIFIC trial compared sequential treatment with the PD-L1 inhibitor durvalumab versus placebo in patients with locally advanced,

unresectable stage III NSCLC who had not progressed following platinum-based chemotherapy concurrent with radiation therapy.

The trial is being conducted at 235 centres in 26 countries, and Dr Scott Antonia from the Moffitt Cancer Center is the lead investigator. It included 713 patients who were randomised 2:1 to receive durvalumab 10 mg/kg every two weeks or placebo for up to 12 months. The co-primary endpoints were progression-free survival and overall survival.

Results from a pre-planned interim analysis at 14.5 months are presented today. The median progression-free survival was 16.8 months in the durvalumab arm compared to 5.6 months with placebo, with a hazard ratio of 0.52.

Paz-Ares said: "Durvalumab decreased the probability of disease progression of 48%. The improvement was consistent across all patient subgroups that were analysed."

The secondary endpoints of time to death or distant metastasis and objective response rate were also improved overall and across subgroups with durvalumab compared to placebo. Overall survival data were immature and and will be analysed after a longer period of follow-up.

Treatment-related adverse events occurred in 68% of patients in the durvalumab group compared to 53% in the placebo group. The rate of immune-mediated adverse events was 24% with durvalumab and 8% with placebo. Severe pneumonitis (grade 3/4) occurred in 3.4% and 2.6% of patients on durvalumab and placebo, respectively. Treatment had to be discontinued due to pneumonitis in 6.3% of patients on durvalumab and 4.3% on placebo.

"Overall there was a slight increase in toxicity in the durvalumab arm but severe toxicity was similar between groups," said Paz-Ares.

He concluded: "Durvalumab is a reasonably well tolerated treatment with a manageable safety profile that improved progression-free survival by 11 months. PD-L1 inhibition after chemoradiation appears to be a new option for patients with locally advanced, unresectable stage III lung cancer. It will be important to see the impact on overall survival after a longer follow-up."

Commenting on the results for ESMO, Dr Pilar Garrido, head of the Thoracic Tumour Section, Medical Oncology Department, Ramón y Cajal University Hospital, Madrid, Spain, said: "PACIFIC is one of the largest clinical trials recruiting patients with unresectable stage III NSCLC. Giving durvalumab after finishing chemoradiation improved progression-free survival by three-fold compared to placebo, which is a clinically relevant benefit. The results for 12 and 18-month progression-free survival were also highly encouraging."

"It is important to highlight the acceptable toxicity profile of durvalumab in this setting, with severe adverse events rates very similar between both arms," she added.

Garrido continued: "Overall survival data are awaited, but the magnitude of progression-free survival benefit supports this combination as a new standard of care for unresectable stage III NSCLC patients who had no progression following standard care with platinum-based chemotherapy and concomitant radiotherapy."

She concluded: "Further research is needed regarding the duration and timing of immunotherapy, the best regimen of chemoradiation to combine it with, and the selection of patients most likely to benefit based on predictive biomarkers."

More information: 1 Abstract LBA1_PR 'PACIFIC: A double-blind, placebo-controlled Phase III study of durvalumab after chemoradiation

therapy (CRT) in patients with Stage III, locally advanced, unresectable NSCLC' will be presented by Dr Luis Paz-Ares during Presidential Symposium I on Saturday, 9 September 2017, 16:30 to 18:10 (CEST) in Madrid Auditorium.

2 Antonia S.J., Villegas A, Daniel D, et al. Durvalumab after Chemoradiotherapy in Stage III Non-Small-Cell Lung Cancer. N Engl J Med. DOI: 10.1056/NEJMoa1709937