OVERALL SURVIVAL RESULTS FROM PACIFIC

TRIAL SUMMARY: Overall and progression-free survival prolonged.

Antonia SJ, Villegas A, Daniel D, et al. Overall survival with durvalumab after chemoradiotherapy in Stage III NSCLC. NEJM, September 25, 2018; presented at WCLC, September 2018, Toronto.

This phase 3 trial compares durvalumab to placebo in patients with stage 3, unresectable non-small cell lung cancer (NSCLC) who did not have disease progression after concurrent chemoradiotherapy. In the study, 473 patients received durvalumab intravenously, at a dose of 10 mg per kilogram of body weight every 2 weeks, and 236 received matching placebo. Randomization occurred 1 to 42 days after the patients had received chemoradiotherapy and was stratified according to age, sex and smoking history. The primary endpoints were progression-free survival (PFS) and overall survival (OS). Secondary endpoints included the time to death or distant metastasis, time to second progression, and safety.

Results: Earlier analysis showed that durvalumab significantly prolonged PFS, as compared with placebo. This analysis presents results on the second primary endpoint of OS. As of March 22, 2018, the median followup was 25.2 months. The 24-month OS rate was 66.3% (95% confidence interval [CI]: 61.7–70.4) in the durvalumab group vs 55.6% (95% CI, 48.9–61.8) in the placebo group (two-sided p=0.005). Durvalumab significantly prolonged OS, as compared with placebo (stratified hazard ratio [HR] for death, 0.68; 99.73% CI, 0.47–0.997; P=0.0025). Updated analyses regarding PFS were similar to those previously reported, with a median duration of 17.2 months in the durvalumab group and 5.6 months in the placebo group (stratified HR for disease progression or death, 0.51; 95% CI: 0.41–0.63). The median time to death or distant metastasis was 28.3 months in the durvalumab group and 16.2 months in the placebo group (stratified HR, 0.53; 95% CI, 0.41–0.68). A total of 30.5% of the patients in the durvalumab group and 26.1% in the placebo group had grade 3 or 4 adverse events of any cause; 15.4% and 9.8% of the patients, respectively, discontinued the trial regimen because of adverse events.

COMMENTARY: Despite multimodality treatment, stage III NSCLC has a poor prognosis, with a median PFS of approximately 8 to12 months following concurrent chemoradiation, and median OS of up to 29 months in trial populations.[1,2,3] For patients who can only tolerate sequential chemoradiation, the outlook is bleaker, with a median OS of just over 12 months.[3]

In 2017, the interim analysis of the PACIFIC trial, comparing durvalumab to placebo after concurrent chemoradiotherapy, focused on PFS and safety reporting.[4] All patients, regardless of programmed death ligand 1 (PD-L1) status, who did not progress after 2 or more cycles of chemoradiation were randomized to receive durvalumab or placebo for up to 1 year. Patients who received durvalumab had a median PFS of 16.8 months vs 5.6 months for patients receiving placebo, with a HR for death or progression of 0.52.

The second co-primary endpoint of OS was reported at the 2018 World Conference on Lung Cancer after a median followup post randomization of 25 months and a planned 299th survival event in March 2018.5 The OS HR was 0.68, representing a 32% reduction in the risk of death and a nearly 11% increase in 2-year survival in the durvalumab arm over placebo. The survival benefit may be underestimated, as it is calculated from date of randomization, which was within 42 days of chemoradiation, and not from date of diagnosis. An improved response rate of 30% with durvalumab vs 17.8% with placebo suggests better local control, as well as better distant control.

Subgroup analysis found that almost all populations of interest appeared to benefit from treatment with durvalumab in the PACIFIC study. Patients receiving cisplatin prior to durvalumab had more benefit than those receiving carboplatin, but this may reflect the tumour biology of patients well enough to receive cisplatin alongside radiotherapy. Tumour tissue was not systematically recorded at enrolment, but was available in approximately two-thirds of patients. An unplanned post-hoc analysis of outcome by tumour PD-L1 status in tissue obtained prior to chemo-

radiation suggests that durvalumab may offer no additional benefit in patients with <1% PD-L1 tumour staining. PD-L1 expression is upregulated by radiation, which suggests that tissue post radiation and prior to durvalumab administration may be more helpful for biomarker evaluation. However, the subgroup analysis did not identify clinical or molecular predictive biomarkers for treatment. Further studies may enable clinicians to identify the population most likely to achieve a significant benefit.

The PACIFIC trial is a breakthrough in the management of stage III NSCLC. For the first time in many years, there is therapy available that improves the chance of cure after chemoradiotherapy. Durvalumab was approved by Health Canada on the basis of the improvement in PFS, and the data presented at the World Conference on Lung Cancer demonstrating OS benefit provides further compelling evidence for the incorporation of durvalumab into the standard of care.

IN BRIEF

Already known

- Stage III NSCLC has a 5-year overall survival (OS) of less than 30% and is likely to recur with metastatic disease despite chemoradiation.

What this study showed

- The addition of maintenance durvalumab for 1 year following chemoradiation not only prolongs the progression-free interval by over 12 months, it also improves median OS. After 25 months, median OS in the durvalumab arm has not yet been reached, while the placebo arm has a median OS of 28.7 months.

Next steps

- 1 year of durvalumab treatment following concurrent chemoradiation is a new standard of care for stage III NSCLC patients.

References

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