First-line Durvalumab Improves Survival Compared to Chemotherapy in Metastatic NSCLC

Two analyses from the MYSTIC study show improved survival supporting the use of front-line durvalumab over chemotherapy in metastatic NSCLC

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Results from two analyses of data from the phase III MYSTIC trial demonstrated that first-line treatment with the anti-PD-L1 monoclonal antibody durvalumab improved overall survival (OS) compared to platinum-based chemotherapy in patients with metastatic non-small cell lung cancer (NSCLC).

Findings presented at the 2019 European Lung Cancer Congress (ELCC), held 10 to 13 April in Geneva, Switzerland, included analyses showing that i) results of the primary OS analysis may have been affected by post-study immunotherapy, ii) favourable HRs for OS were observed across subgroups with durvalumab versus chemotherapy, and iii) durvalumab with or without the anti-CTLA-4 antibody tremelimumab was associated with fewer high-grade treatment-related adverse events than chemotherapy.

Both analyses used data from the phase III, randomised, open-label**,** MYSTIC study (NCT02453282) of first-line durvalumab with or without tremelimumab compared to chemotherapy in patients with metastatic NSCLC.

The previously reported primary analysis of MYSTIC data showed a clinically meaningful improvement in OS with first-line durvalumab versus chemotherapy in patients with metastatic NSCLC and tumour cell (TC) PD-L1 expression ≥25% (hazard ratio [HR], 0.76; 97.54% confidence interval [CI], 0.56–1.02; p = 0.036**).**

However, the OS findings did not reach statistical significance.

The trial enrolled immunotherapy/chemotherapy-naïve patients with metastatic NSCLC who were randomised equally to receive durvalumab monotherapy at 20 mg/kg every 4 weeks until disease progression; or durvalumab at 20 mg/kg every 4 weeks until disease progression plus tremelimumab at 1 mg/kg every 4 weeks for 4 cycles; or up to 6 cycles of platinum-based chemotherapy.

In-study crossover from chemotherapy to either of the durvalumab arms was not allowed, but subsequent post study treatment was recorded.

Exploratory analysis demonstrates improved OS with durvalumab after correcting for post study immunotherapy

Niels Reinmuth of the Asklepios Lung Clinic in Munich-Gauting, Germany and a team of investigators explored whether subsequent immunotherapy received primarily by patients in the chemotherapy arm may have confounded the primary OS results and masked the true efficacy of durvalumab.

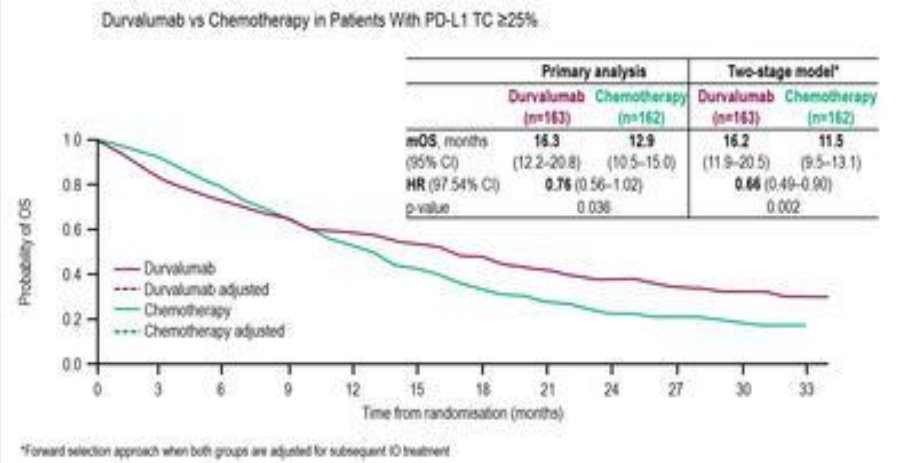
In this exploratory analysis, the investigators used three statistical models to assess the effect of subsequent immunotherapy on OS in the durvalumab monotherapy and chemotherapy arms in the primary analysis population of patients with PD-L1 TC ≥25%: the rank preserving structural failure time (RPSFT) method, the inverse probability of censoring weighting (IPCW) method, and a two-stage method.

Subsequent immunotherapy was received by more patients in the chemotherapy arm than in the durvalumab arm

As of 4 October 2018, subsequent treatment had been received by 73 (44.8%) patients in the durvalumab arm compared to 95 (58.6%) patients in the chemotherapy arm. A total of 25 (15.3%) patients in the durvalumab arm and one (0.6%) patient in the chemotherapy arm remained on study treatment.

Of the group who received subsequent treatment, immunotherapy was administered to 10 (13.7%) patients in the durvalumab arm and 64 (67.4%) patients in the chemotherapy arm. The most commonly administered subsequent immunotherapies were nivolumab and pembrolizumab, which were received by 1.8% and 2.5%, respectively, of all patients originally randomised to durvalumab, and by 30.9% and 6.8% of all patients originally randomised to chemotherapy. Other immunotherapies received included atezolizumab, durvalumab (chemotherapy arm only), or tremelimumab (chemotherapy arm only). Cytotoxic chemotherapy was administered to 42.9% of patients in the durvalumab arm and 35.8% of patients in the chemotherapy arm.

The investigators found that the two-stage method was the most appropriate for evaluating the effect of subsequent immunotherapy on OS. **By this method, durvalumab significantly improved OS compared to chemotherapy (HR, 0.66 [97.54% CI, 0.49–0.90]; p = 0.002]).**



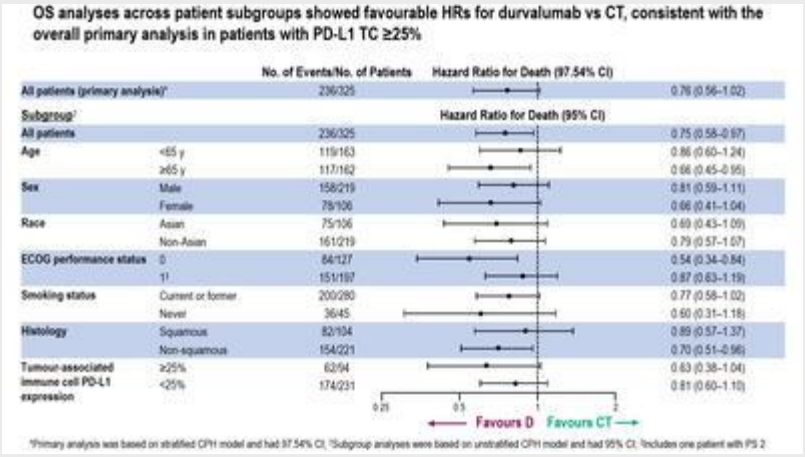
Increased OS benefit with first-line durvalumab vs chemotherapy was observed after adjusting for the effect of subsequent IO using the two-stage model

Subgroup analysis demonstrates durvalumab benefit across a range of patient characteristics

The subgroup analysis performed by Byoung Chul Cho of the Yonsei Cancer Centre, Yonsei University College of Medicine in Seoul, Republic of Korea and colleagues included 488 patients with PD-L1 TC ≥25%; 163 patients in the durvalumab monotherapy arm, 163 patients in the durvalumab plus tremelimumab arm, and 162 patients in the chemotherapy arm. Baseline characteristics were balanced between treatment arms. The investigators assessed OS according to baseline clinical characteristics that included the following prespecified variables: age, gender, race, histology, smoking history, and tumour-associated immune cell (IC) PD-L1 expression (≥25% versus <25%). ECOG performance status was also included as a post-hoc variable.

Durvalumab alone resulted in improvement in OS compared to chemotherapy across most clinical subgroups, including age ≥65 years (HR, 0.66 [95% CI, 0.45–0.95]), non-squamous histology (HR, 0.70 [95% CI, 0.51–0.96]), PD-L1 IC ≥25% (HR, 0.63 [95% CI, 0.38–1.04]), and ECOG performance status 0 (HR, 0.54 [95% CI, 0.34–0.84]).

Durvalumab plus tremelimumab provided similarly improved OS compared to chemotherapy in these subgroups: age ≥65 years (HR 0.72 [95% CI, 0.50–1.02]), non-squamous histology (HR, 0.84 [95% CI, 0.61–1.14]), PD-L1 IC ≥25% (HR 0.64 [95% CI, 0.39–1.05]), and performance status 0 (HR 0.76 [95% CI, 0.50–1.14]).



OS analyses across patient subgroups showed favourable HRs for durvalumab vs CT, consistent with the overall primary analysis in patients with PD-L1 TC ≥25%

The durvalumab plus tremelimumab arm showed the highest rates of treatment-related adverse events (TRAEs) leading to discontinuation and immune-mediated AEs (imAEs). The rates of any TRAEs leading to discontinuation with durvalumab, durvalumab plus tremelimumab, and chemotherapy were 5.4%, 13.2%, and 9.4%, respectively, and the rates of any imAE in the respective groups were 13.6%, 28.3%, and 3.4%. The most commonly reported TRAEs leading to discontinuation in the respective cohorts were pneumonitis (0.8%,1.9%, and 0.3%), and interstitial lung disease (0.5%, 1.3%, and 0.3%). The most frequently reported imAEs were hypothyroidism and pneumonitis, which occurred at rates of 5.7% and 2.2%, respectively, with durvalumab, 7.5% and 6.7% with durvalumab plus tremelimumab, and 0.6% and 1.4% with chemotherapy.

Patients treated with chemotherapy had the highest rates of grade ≥3 TRAEs; the rates for the occurrence of grade ≥3 TRAEs were 14.9% with durvalumab, 22.9% with durvalumab plus tremelimumab, and 33.8% with chemotherapy. The most commonly occurring grade ≥3 TRAEs in the chemotherapy arm were anaemia (10.2%) and neutropenia (9.9%).

Conclusions

The authors of the exploratory analysis of the effect of post-study immunotherapy on OS in the MYSTIC study concluded that a high proportion of patients in the chemotherapy arm received subsequent immunotherapy. They proposed that this subsequent immunotherapy may have confounded the primary OS outcome. Their analysis demonstrated an increased OS benefit with first-line durvalumab compared to chemotherapy after adjusting for the effect of subsequent immunotherapy.

The authors of the subgroup analysis of MYSTIC study data concluded that the OS analyses across patient subgroups showed favourable HRs for durvalumab compared to chemotherapy across most patient subgroups that were consistent with the overall primary analysis. The safety profile of durvalumab with or without tremelimumab was consistent with previous studies, with lower rates of grade ≥3 TRAEs than chemotherapy.

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