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Editorial

Different interpretations of the CheckMate-227 trial in non-small-cell lung cancer

In the CheckMate-227 phase 3 trial [1], non-small-cell lung cancer (NSCLC) patients with stage IV or recurrent NSCLC and a PD-L1 expression level of ≥1% were randomized in a 1:1:1 ratio to receive nivolumab plus ipilimumab, nivolumab alone, or chemotherapy. Patients with a PD-L1 expression level of less than 1% were randomly assigned in a 1:1:1 ratio to receive nivolumab plus ipilimumab, nivolumab plus chemotherapy, or chemotherapy alone.

The primary endpoint of the trial was overall survival with nivolumab plus ipilimumab as compared with chemotherapy in patients with a PD-L1 expression level of ≥1%. Hierarchical secondary endpoints were progression-free survival with nivolumab plus chemotherapy as compared with chemotherapy in patients with a PD-L1 expression level of less than 1%; overall survival with nivolumab plus chemotherapy as compared with chemotherapy in patients with a PD-L1 expression level of less than 1%; and overall survival with nivolumab monotherapy as compared with chemotherapy in patients with a PD-L1 expression level of ≥50%. The second endpoint in the hierarchy failed to reach statistical significance. As a result, formal statistical testing of the last secondary endpoint was not conducted.

Nivolumab plus ipilimumab, as compared with chemotherapy, was further evaluated in a prespecified descriptive analysis of patients with a PD-L1 expression level of less than 1% and in all the trial patients. In patients with a PD-L1 expression level of less than 1%, the median duration of overall survival was 17.2 months with nivolumab plus ipilimumab and 12.2 months with chemotherapy. Among all the patients in the trial, the median duration of overall survival was 17.1 months with nivolumab plus ipilimumab and 13.9 months with chemotherapy.

The conclusions section of the abstract states that "First-line treatment with nivolumab plus ipilimumab resulted in a longer duration of overall survival than did chemotherapy in patients with NSCLC, independent of the PD-L1 expression level." As stated in The New England Journal of Medicine's new guidelines for statistical reporting [2]: "it is important to adhere to a prespecified analysis plan if one exists; the use of statistical thresholds for claiming an effect or association should be limited to analyses for which the analysis plan outlined a method for controlling type I error". The conclusion that nivolumab plus ipilimumab resulted in a longer duration of overall survival independent of the PD-L1 expression level is based on a descriptive analysis without formal statistical testing, which is inconsistent with the journal's own guidelines.

On January 31, 2020, Bristol-Myers Squibb Company announced that it has withdrawn its application in the European Union for the combination of nivolumab and ipilimumab for the treatment of NSCLC based on data from the CheckMate-227 trial. Though the Committee for Medicinal Products for Human Use (CHMP) acknowledged the integrity of the patient level data, the CHMP determined a full assessment of the application was not possible following multiple protocol changes the company made in response to rapidly evolving science and data [3].

On May 15, 2020, the Food and Drug Administration (FDA) approved the combination of nivolumab plus ipilimumab as first-line treatment for patients with NSCLC whose tumors express PD-L1 (≥1%), with no epidermal growth factor receptor (EGFR) or anaplastic lymphoma kinase (ALK) genomic tumor aberrations [4].

Different interpretations of the CheckMate-227 trial were reached by the FDA, the CHMP and a leading medical journal. The combination of nivolumab and ipilimumab demonstrated highly encouraging results in patients with NSCLC, independent of the PD-L1 expression level. Conclusions should be based on the prespecified statistical analysis plan that controls the Type I error rate. The combination therapy has the potential to benefit NSCLC patients with a PD-L1 expression level of less than 1%, and further studies may shed additional light on its role in prolonging the lives of patients with NSCLC across the globe.

References

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