Nivolumab Past One Year Improves Progression-Free Survival in Pretreated NSCLC

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Continuous treatment with nivolumab until disease progression was associated with superior progression-free survival (PFS) compared with a 1-year fixed duration treatment for patients with previously treated advanced non-small cell lung cancer (NSCLC).[1]

In CheckMate-153, among the patients still on nivolumab at 1 year of the study, those who were treated continuously had significantly improved PFS compared with those who stopped nivolumab (hazard ratio [HR], 0.43; 95% CI, 0.25-0.76), David R. Spigel, MD, chief scientific officer at Sarah Cannon Research Institute/Tennessee Oncology. Spigel presented the findings at the 2017 ESMO Congress in Madrid. PFS was a prespecified exploratory objective of CheckMate-153.

There was also a trend toward improved overall survival (OS) favoring continuous nivolumab, with follow-up for OS ongoing. “The optimal duration of treatment with any checkpoint inhibitor, PD-1 or PD-L1 inhibitor, remains an unknown important question,” Spigel said. “CheckMate-153 is the first randomized study to evaluate treatment duration with a PD-1 or PD-L1 inhbitor.”

Nivolumab is the standard of care for previously treated NSCLC, with a 5-year OS rate of 16%. Most outcomes data with nivolumab are based on treatment until the patient experiences disease progression or stops therapy due to unacceptable

toxicity.

The phase I CheckMate-003 study involving patients with previously treated NSCLC implemented a stopping rule for nivolumab at 96 weeks. Study results showed that nivolumab monotherapy for a duration of 96 weeks produced long-term clinical benefit; 75% of patients who were alive >5 years remained on treatment and progression-free while just 25% of patients alive >5 years stopped nivolumab earlier than the 96 week-rule due to an adverse event.

CheckMate-153 is an ongoing phase IIIb/IV study. Patients who had undergone at least 1 previous systemic treatment for advanced or metastatic NSCLC and remained on 3 mg/kg nivolumab every 2 weeks for 1 year were randomly assigned to continue receiving nivolumab until progressive disease or unacceptable toxicity or to discontinue treatment. Resumption of nivolumab was allowed at disease progression in the stop arm.

The primary objective was the incidence of high-grade (grade 3-5) selected treatment-related adverse events. Prespecified exploratory endpoints included safety and efficacy.

Of the 1245 patients enrolled, 220 remained on treatment for 1 year and were randomized in a 1:1 fashion to continuous nivolumab or termination of nivolumab regardless of response status. Patients who had a complete response (CR), partial response (PR), or stable disease (SD) at randomization (n = 76 in the continuous nivolumab arm; n = 87 in the arm that stopped nivolumab treatment at 1 year) were eligible for efficacy analyses. Safety analyses were based on all 220 patients, 107 in the continuous arm and 113 in the stop arm.

More than 95% of the patients in each arm were smokers. In patients who had biopsy tissue collected, PD-L1 status percentage was balanced between the arms.

Many patients in the study were heavily pretreated. Spigel said that roughly one-quarter of the cohort had four or more prior lines of therapy at enrollment.

There was a higher percentage of patients with squamous histology in the 1-year treatment arm compared with the continuous arm (47% vs 34%). Seventy percent of patients in the continuous treatment arm and 56% in the 1-year treatment arm had CR/PR prior to randomization.

Median PFS from randomization was 10.3 months in the 1-year treatment arm, with optional retreatment allowed at progressive disease, and was not reached in the

continuous treatment arm. The 6-month PFS rate was 69% in the 1-year arm and 80% in the continuous arm. The 1-year PFS rate was 40% and 65%, respectively.

When stratified by response status prior to randomization, there was no difference in the HR for PFS from randomization between those who had a CR/PR and those who had SD. Among patients with CR/PR, the median PFS was 10.6 months in the 1-year treatment arm and was not reached in the continuous arm (HR, 0.45; 95% CI 0.24-0.85). Among patients with SD as best response, median PFS was 96 months in the 1-year treatment arm and not reached in the continuous arm (HR, 0.44; 95% CI 0.17-1.09). The PFS advantage favored continuous nivolumab in all subgroups examined, including subgroups stratified by PD-L1 expression.

There was a trend toward improved OS in the continuous treatment arm. Median OS was 23.2 months in the 1-year treatment arm and was not reached in the continuous treatment arm (HR, 0.63; 95% CI, 0.33-1.20). The OS rate at 1 year was 88% in the arm randomized to continuous treatment compared with 81% in the 1-year treatment arm.
Of the 87 patients randomized to stop nivolumab at 1 year, 43 (49%) had progressive disease after stopping, and 34 (79%) were retreated with nivolumab. In these 34 patients, the median time between documented progression and retreatment was 0.6 months. The median duration of retreatment was 3.8 months. Twelve of the 34 patients (35%) who underwent retreatment had progressive disease in target lesions only. In assessing tumor burden change in target lesions following retreatment, Spigel said, “There are some patients . . . who maintain benefit in the form of disease control even over several months.”

Subsequent systemic therapy was administered to 29% of patients in the 1-year treatment arm and 13% in the continuous arm. Researchers observed a slightly higher rate of treatment-related adverse events (TRAEs) in the continuous treatment arm (39% vs 25%), as well as grade 3-4 events (8% vs 4%).

“There were few new-onset events after 1 year,” Spigel said. “There were no treatment-related deaths occurring in any of the patients in either arm. There were no new safety signals identified in either arm.”

The question of optimal duration of immune checkpoint blockade in NSCLC is too important to be left to exploratory endpoints, said discussant Martin Reck, MD, from LungenClinicGrosshansdorf, Germany. He said the issue should be addressed in a prospective randomized trial with adequate statistical design.

1. Spigel D, McLeod M, Hussein M, et al. Randomized results of fixed-duration (1-yr) vs continuous nivolumab in patients (pts) with advanced non-small cell lung cancer (NSCLC). Presentedat ESMO 2017 Congress; September 8-12, 2017; Madrid, Spain. Abstract 1297O.