Expert Perspectives

The Revised NCCN Guidelines for Non-Small Cell Lung Cancer

Durvalumab: A New Option for Patients with Stage III Non-Small Cell Lung Cancer

One of the most striking updates to the NCCN 2017 Guidelines is the recommendation of durvalumab as a treatment option for patients with stage III non-small cell lung cancer (NSCLC) after definitive chemoradiation (Table 1).[1] Clinicians immediately knew the therapy would change the standard of care for locally-advanced NSCLC when the clinical trail results were first reported at the European Society for Medical Oncology 2017 Congress this fall. “There really hasn't been a major change in our management of stage III NSCLC in more than a decade. That changed today” reflected H. Jack West, MD, Medical Director of the Thoracic Oncology Program at the Swedish Cancer Insittute.[2]

Table 1. Addition of Durvalumab in the National Comprehensive Cancer Network Clinical Practice Guidelines, 2017*

Additional therapy for stage III NSCLC

- Following studies showing its effectiveness as a consolidation therapy in stage III NSCLC patients after chemotherapy, durvalumab has been added as a treatment option after definitive chemoradiation (category 2A)

Principles of treatment with durvalumab

- Durvalumab is a human IgG1 monoclonal antibody that inhibits the binding of programed death ligand 1 (PD-L1) to programed death 1 (PD-1) and CD80, enabling T cells to identify and then destroy tumor cells.
- Durvalumab may be especially effective following chemotherapy and radiation because these treatments increase PD-L1 expression in tumor cells.

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* NCCN Guidelines Version 9.2017. NSCLC. Available at https://www.nccn.org/professionals/physician_gls/pdf/nscl.pdf. Accessed October 31, 2017.

Previously, oncologists often prescribed additional therapy after the conclusion of chemotherapy and radiation. “[This treatment plan] is actually permitted in various guidelines that are available, despite the fact that there are no data suggesting that more chemotherapy [is beneficial],” said Dr. Mark Kris, MD, from Memorial Sloan Kettering in New York City. “Durvalumab is an alternative to that approach, and one that has been shown to work in a large randomized trial.”[3]

Durvalumab (Imfinzi™) is a human IgG1 monoclonal antibody that selectively inhibits the binding of programed death ligand 1 (PD-L1) to programed death 1 (PD-1) and CD80. This inhibition enables T cells to identify and then destroy tumor cells. Early clinical studies with the therapy with different types of tumors suggested a promising efficacy and safety profile. Part of the reason for the therapy’s effectiveness could be that the expression

levels of PD-L1 in tumor cells are actually thought to be upregulated in patients following chemotherapy and radiotherapy according to preclinical evidence.[4]

The guideline updates were inspired by the PACIFIC phase 3 randomized trial that compared consolidation therapy with durvalumab to placebo in over 700 patients with unresectable stage III NSCLC who had not progressed after at least two cycles of chemotherapy followed by chest radiation. Patients were randomly assigned durvalumab or placebo in a 2:1 ratio within 1 to 42 days after chemoradiotherapy. Patients received either the study drug or the placebo intravenously every 2 weeks for up to a full year.[1, 4]

The results were encouraging and demonstrated that durvalumab had a superior efficacy to the placebo. The study drug had a superior progression free survival (PFS) of 16.8 months versus 5.6 months for the placebo (hazard ratio, 0.52; confidence interval, 0.42-0.65; *P*<.001). Durvalumab also had a higher response rate of 28.4% compared to16% with the placebo (*P*<.001). Similarly, the drug had a significantly longer median time of death or distant metastasis of 23.2 months versus 14.6 months for the placebo (*P*<.001). Furthermore, the rate of grade 3 or 4 adverse events was comparable between the two groups (durvalumab, 29.9% vs. placebo, 26.1%), and pneumonia was the most common grade 3 or 4 adverse events (durvalumab, 4.4% vs. placebo, 3.8%).[1, 4] Most of the patients in the study did not have EGFR mutations and were either current or former smokers. They also typically had an unknown or less than 25% PD-L1 status.[1, 4]

“[This therapy] didn't disappoint,” West said. “Although there has been some back and forth discussion about the significance of results that don't include [overall survival], particularly in a potentially curative setting, the prevailing view has been the one I share, that these results are remarkably impressive and warrant a change in the standard of care.”[2] The NCCN Guidelines were updated shortly after the publication and international conference presentation detailing the results from the clinical trial.

Ongoing and Follow-Up Studies with Durvalumab

The clinical success of durvalumab has motivated a number of ongoing and upcoming studies examining other uses in the drug as a monotherapy or in combination with different treatments in NSCLC patients.

For example, the ongoing MYSTIC (NCT02453282) and NEPTUNE (NCT02542293) phase 3 trials are examining durvalumab as a frontline monotherapy or as a combination therapy with tremelimumab. Meanwhile another ongoing study still recruiting patients is examining durvalumab as an adjuvant for patients with completed resected cancer (NCT02273375). A phase 3 trail investigating durvalumab in combination with epacadostat in patients with locally-advanced, unresectable non-small cell lung cancer is also set to begin in

early 2018.[5] These and other collective ongoing studies may further dramatically shift the treatment landscape for a wide range of NSCLC patients.

References

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