Expert Perspectives

The Revised NCCN Guidelines for Non-Small Cell Lung Cancer

New Options for Patients with ALK and BRAF Alterations

The landscape for the targeted treatment of non-small cell lung cancer (NSCLC) is rapidly changing. Some NSCLC patients have specific biomarkers that make them excellent candidates for therapies that can be more effective and less toxic than traditional chemotherapy.

Two important biomarkers associated with targeted therapies are the anaplastic lymphoma kinase (ALK) gene and the BRAF (v-RAF murine sarcoma viral oncogene homolog B) gene. The NCCN Guidelines have recently been updated to reflect new treatment options for patients with alterations in these genes (Table 1).

New Options for Patients with ALK Alterations

The ALK gene codes for a transmembrane tyrosine kinase, and alterations in this gene are found in approximately 5% of patients with adenocarcinoma.[1] Most mutations associated with the ALK gene involve a fusion with some type of partner gene. There are approximately 30 known ALK fusions and they are generally mutually exclusive to EGFR mutations. Patients with these alterations can be excellent candidates for ALK inhibitors, including ceritinib, alectinib, crizotinib, and brigatinib.[1]

One important update to the new NCCN Guidelines includes the use of ceritinib (Zykadia®) for patients with ALK-positive NSCLC. The therapy was already included in previous versions of the guidelines as a subsequent treatment for ALK-positive NSCLC patients that had progressed after crizotinib. However, the NCCN guidelines have now been updated to include ceritinib as a frontline therapy for ALK-positive NSCLC patients based on the results of the ASEND-4 phase 3 trial comparing ceritinib to platinum based chemotherapy as a first-line option. The study showed a promising progression free survival of 16.6 months for ceritinib compared to 8.1 months for chemotherapy (P<.00001). Common adverse events for ceritinib included nausea, diarrhea, vomiting, and an increase in alanine aminotransferase.[2]

Similarly, alectinib (Alecensa®) was already included in the NCCN guidelines as a subsequent therapy for NSCLC patients with ALK alterations that had progressed after crizotinib. The NCCN Guidelines have been updated this year to include alectinib as a first-line option for metastatic NSCLC patients with ALK alterations based on results from the ALEX phase 3 trial. In fact, the trial results were encouraging enough for NCCN panel members to vote alectinib as the preferred first-line agent for metastatic ALK-positive NSCLC patients. The trial compared alectinib to crizotinib as a first-line option in 303 patients with advanced NSCLC that had ALK alterations. Patients receiving alectinib had a more promising response rate of 83% compared to 75% for crizotinib. Fewer patients also progressed on alectinib (41% with a median follow-up of 18.6 months) compared to crizotinib (68% with a median follow-up of 17.6 months). Additionally, alectinib had a more promising progression free survival of 68.4% compared to 48.7% for crizotinib. Alectinib also had fewer serious adverse events compared to crizotinib despite their longer therapy duration.[1]

Table 1. New Options for Patients with ALK and BRAF Alterations in the National Comprehensive Cancer Network Clinical Practice Guidelines, 2017*

Additional therapies for patients with ALK Alterations

- Following results from a phase 3 trail showing its effectiveness as frontline option, ceritinib has been added as a first-line treatment option for patients with ALK alterations (category 1)
- Following results from a phase 3 trial showing its effectiveness as a frontline option, alectinib has been added as a first-line treatment option for patients with ALK alterations (category 1)
- Following results from the same trial, NCCN panel members also voted alectinib as the preferred first-line agent for metastatic ALK-positive NSCLC patients (category 1)
- Following FDA approval and results from a phase 2 trial, brigatinib has been added as a subsequent therapy for patients with ALK alterations that have progressed after crizotinib (category 2A)

New Options for patients with BRAF Alterations

- Following studies and FDA approval, combination therapy with dabrafenib and trametinib is recommend as a first-line treatment for patients with the BRAF V600E mutation (category 2A)
- Monotherapy with vemurafenib or dabrafenib have been added as options when combination therapy is not tolerated (category 2A)

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

"Something else of important note is that patients who received alectinib had a very large benefit with CNS metastases," said Victoria M. Villaflor, MD, an associate professor of medicine at Robert H. Lurie Comprehensive Cancer Center in the Feinberg School of Medicine at Northwestern University. "This was both in response to alectinib, plus it also took longer until they progressed in the CNS because of the inability to pass the blood-brain barrier."[3]

The NCCN also recently updated their guidelines to include the TKI therapy brigatinib (Alunbrig™) as a subsequent therapy for patients with ALK alterations that have progressed after crizotinib. The guideline updates were motivated by the FDA approval of the drug for patients with ALK-positive metastatic NSCLC and results from the recent ALTA phase 2 trail. Results from the trial showed response rates of 45% in patients with 90 mg daily dose and 54% in patients with a 180 mg daily dose of brigatinib. Response rates were also promising in patients with measurable brain metastasis (90 mg dose, 42%; 180 mg dose, 67%). Serious adverse events included hypertension and pneumonia.[1]

Finally, crizotinib (Xalkori®) remains an effective first-line option for patients with ALK rearrangements, and the NCCN Guidelines have also been updated this year to further highlight its dual effectiveness as an option for patients with ROS1 rearrangements. This update is based on the FDA approval of crizotinib for the treatment of patients with ROS1 rearrangements and the recent finding that showed therapy with crizotinib had a response rate of 70% in patients ROS1 rearrangement-positive NSCLC.[1]

New Options for Patients with BRAF Alterations

The BRAF gene encodes the B-RAF protein that participates in cellular signalling pathways. The most common mutation associated with the gene produces the protein B-RAF V600E, and this mutation is found in 1-4% of patients with adenocarcinoma.[1] New treatments have recently been discovered that could benefit patients with the mutation.

The combination regimen of dabrafenib/trametinib is the only approved targeted first-line therapy for patients with the BRAF V600E mutation. Dabrafenib (Tafinlar®) is a tyrosine kinase inhibitor (TKI) that inhibits BRAF V6000E mutations while trametinib (Mekinist®) can inhibit both BRAF V600E and Mitogen-activated protein kinase kinase (MEK).

The NCCN guideline updates were based on a phase 2 non-randomized study conducted in patients with the BRAF V600E mutation. Patients had an excellent response rate to the drug as both a first-line and subsequent therapy. Those that received the combination therapy as a first-line treatment had a response rate of 64% while those that received the duo as a subsequent therapy after previous treatment with a platinum-based chemotherapy had a response rate of 63%.[4-5]

However, the therapy also had a higher toxicity. Approximately 69% of patients that received the combination therapy as a first-line and 56% that received the treatment as a subsequent therapy experienced a serious adverse events, including pyrexia, hemoptysis, cutaneous squamous cell carcinoma, pyrexia, anemia, and a confused state.[4-5] Although the combination therapy has a higher

toxicity than some other existing therapies, many clinicians maintain the combination therapy's benefits are worth the side effects.

"Many of us would, in this situation, characterize [the therapy's toxicity] as manageable. Again, we've had this regimen out in the melanoma population, and it's used quite frequently in that population," says Mark A. Socinski, MD, who serves as the Executive Medical Director of the Florida Hospital Cancer Institute. "I'm thinking, in the majority of the cases, [the toxicity] will be more of an inconvenience than it is a reason that the patient can't continue on treatment."[6]

When patients are unable to tolerate the combination therapy, single therapy with dabrafenib or vemurafenib (Zelboraf®) can also be effective and is recommended in the NCCN Guidelines.

Indeed, despite adverse events, the efficacy of these new therapies has motivated the NCCN Guidelines to categorize BRAF V600E as a standard biomarker. The guidelines now recommend that clinicians regularly test for the mutation as part of a broader molecular profiling effort looking at standard biomarkers. The biomarker should be regularly tested in patients with adenocarcinoma and should be considered for testing in patients with squamous cell carcinoma.[1]

References

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