Expert Perspectives

The Revised NCCN Guidelines for Non-Small Cell Lung Cancer

Osimertinib: A New Frontline Option for EGFR Mutation-Positive Patients

Recent advances in targeted therapies have provided a new treatment option for EGFR-mutation positive patients with non-small cell lung cancer (NSCLC). The new treatment—osimertinib (Tagrisso®)—represents an exciting frontline option that may have a substantially lower risk for the development of treatment resistance (Table 1).

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

Osimertinib as a targeted therapy for EGFR-positive NSCLC

- Following results from clinical studies showing its effectiveness in metastatic NSCLC, osimertinib has been added as a first-line treatment option for patients with ALK alterations (category 2A)
- Following clinical studies showing its effectiveness in metastatic NSCLC, osimertinib has added as a subsequent therapy after progression on erlotinib, afatinib, or gefitinib (category 1)

Principles of treatment with osimertinib

- Patients with EGFR-mutated cancers are optimal candidates for EGFR-TKI targeted therapies that can be more effective and less toxic than traditional chemotherapy.
- Patients frequently develop resistance to common EGFR-TKI therapies during treatment. This may be due to the acquisition of the EGFR T790M mutation.
- Osimertinib selectively targets common EGFR mutations and the EGFR T790M mutation, providing an effective new frontline treatment option that may be less prone to acquired resistance.

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

The EGFR gene encodes the epidermal growth factor receptor protein, and most mutations associated with the gene result in constitutively activated protein. Overexpressed protein leads to uncontrolled cellular growth and tumor formation. In fact, overexpression of EGFR has been linked to tumors in the lung, prostate, kidney, colon, ovary, and bladder.[1] Mutations in this gene are the second most commonly identified type of mutation associated with lung cancer and can be found in up to 50% of patients with adenocarcinoma.[2]

"[The] EGFR mutation is predictive for response and prognostic for survival," said Wallace Akerley, MD, Director of the Thoracic Program in the Huntsman Cancer Institute at the University of Utah and a member of the NCCN Non–Small Cell Lung Cancer (NSCLC) Panel. "In my opinion, EGFR-mutated and EGFR wild-type NSCLC are 2 distinct cancers, as different as breast and colon cancer."[3]

The majority of EGFR mutations are in exons 18-21, the portion of the gene responsible for encoding the tyrosine kinase domain. These mutations are associated with increased sensitivity to EGFR TKI therapy, like gefitinib, erlotinib, or afatinib.[1] However, sometimes patients develop resistance to these therapies during treatment. Part of the reason for treatment resistance could be the development of an additional EGFR gene mutation in exon 20. This mutation, T790M, replaces the "gatekeeper residue" threonine with a bulkier methionine that interferes with the binding of EGFR TKI therapeutics. This mutation is consequently found in over 50% of patients with acquired resistance to EGFR TKI therapeutics.[1]

"Osimertinib, a third-generation TKI, affects the same *EGFR* sensitivity mutations plus the T790 mutation, the acquired mutation that is the most common cause of eventual resistance to first- and second-generation TKIs," Akerley said. "Additionally, it has less effect on wild-type *EGFR* of the gut and skin, so adverse effects are minimized."[3]

Two recent reports inspired the NCCN guideline changes. The phase 1 AURA study examined the efficacy and safety osimertinib as a first-line treatment in 60 patients with locally advanced or metastatic NSCLC with EGFR mutations. The treatment had a promising objective response rate, progression free survival, and safety profile.[4] Similarly, positive updates from the phase 3 FLAURA clinical trial examining the safety and efficacy of osimertinib as a first-line therapy for patients with EGFR mutation-positive NSCLC were recently reported at an international conference.[5] The trail randomized 556 patients in a 1:1 ratio to osimertinib or an EGFR-TKI therapy (erlotinib or gefitinib). Patients treated with osimertinib had a lower incidence of grade 3 or higher adverse events when compared to standard treatments (osimertinib, 34% vs. standard treatment, 45%). Patients treated with osimertinib also had a longer median progression-free survival than the standard of care (osimertinib, 18.9 months vs. standard therapy, 10.2 months; $P<0.0001$).

"The progression-free survival benefit for patients with and without brain metastases was almost identical, suggesting that osimertinib is active in the brain as well as in systemic sites. This is important because brain metastasis is a common problem in EGFR mutated patients" said Professor Suresh Ramalingam, MD, Deputy Director at the Winship Cancer Institute of Emory University and the principal investigator of the study.[5]

In addition to being recommended as a first-line therapy in the NCCN guideline update, the medication is also recommended for subsequent treatment of patients with EGFR T790M mutations that have developed resistance for other first-line options.[2]

"I will definitely be inclined to switch as many of my current patients on erlotinib to osimertinib as soon as is feasible, as well as start my newly diagnosed patients with an activating EGFR mutation on osimertinib," reflected H. Jack

West, MD, Medical Director of the Thoracic Oncology Program at the Swedish Cancer Insittute hearing the results of the clinical study that inspired the guideline change at a recent conference. “[This treatment is] another game changer.”[6]

Ongoing and Follow-Up Studies with Osimertinib

Osimertinib has drastically changed the standard of care for EGFR-positive NSCLC. However, more work still needs to be done examining this therapy.

“Overall survival data is not yet mature and there is a clear need to continue follow-up to see if those treated with osimertinib live longer,” reflected Enriqueta Felip, MD, PhD, with the Head, Thoracic and H&N Cancer Group at Vall d'Hebron University Hospital. “More data is needed on the mechanisms of acquired resistance in patients treated with osimertinib in the first line setting.”[7]

Ongoing clinical trials with the medication as a monotherapy and as a combination therapy may further change the treatment landscape. For example, the ongoing BOOSTER phase 2 trial is comparing the efficacy of osimertinib on its own and in combination with the monoclonal antibody bevacizumab in patients with advanced NSCLC (NCT03133546).

The therapy is also being examined alongside savolitinib, a c-MET receptor tyrosine kinase selective inhibitor. Two phase 1b/2 proof-of-concept studies showed that the combination therapy can be effective in patients that have progressed after treatment with an EGFR inhibitor alone.[8-9]

References

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