Targeted/Emerging Therapies for Metastatic Non–Small Cell Lung Cancer

Presented by Leora Horn, MD, MSc

Abstract
At one time, histology alone guided treatment decisions in non-small cell lung cancer (NSCLC), but now molecular diagnostics help to categorize patients with lung cancer by driver mutations. This additional information arms oncologists with the keys to selecting the right targeted agent with the best chance of success for different subgroups of patients with NSCLC. During her presentation at the NCCN 20th Annual Conference, Dr. Leora Horn focused attention on both approved and emerging therapies in metastatic disease that target an assortment of molecular subsets, such as EGFR mutations, ALK rearrangements, ROS1 rearrangements, and BRAF mutations. (J Natl Compr Canc Netw 2015;13:676–678)

"We have had the greatest improvements over the past decade in patient outcomes in adenocarcinoma," declared Leora Horn, MD, MSc, Associate Professor of Medicine, Department of Hematology Oncology; Clinical Director, Thoracic Oncology Research Program; and Assistant Director, Educator Development Program, Vanderbilt University. As for adenocarcinoma, slow progress is being made, as several driver mutations (Figure 1) and corresponding targeted agents are currently under study, added Dr. Horn, who is a panel member of the NCCN Guidelines Panel for Non–Small Cell Lung Cancer (NSCLC).

Moving From Histology to Molecular Diagnostics
The traditional view of NSCLC was to categorize disease by histologic subtypes, such as adenocarcinoma, squamous cell carcinoma, and large cell carcinoma. However, molecular testing now provides essential additional information on a patient's tumor and how best to target it therapeutically.

According to the 2015 NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines) for metastatic NSCLC, the first step is to establish a histologic subtype with adequate tissue for molecular testing. Then, if the histology is adenocarcinoma, large cell carcinoma, or NSCLC not otherwise specified, epidermal growth factor receptor (EGFR) and anaplastic lymphoma kinase (ALK) mutational testing is a category 1 recommendation. If the histology is squamous cell carcinoma, the NCCN Guidelines suggest that both EGFR and ALK mutational testing be considered, especially in those who have never smoked.

Targeting EGFR Mutations: First-Line and Beyond
Ranking behind KRAS mutations as the second largest cohort of molecular subsets of lung cancer, EGFR mutations have changed the way that NSCLCs are currently treated. Although Dr. Horn admitted that no effective therapies are available at this time for patients with KRAS mutations, several worthwhile options exist for those with EGFR mutations. Both erlotinib and afatinib are category 1 recommendations as first-line options for patients with EGFR mutations.

Dr. Horn briefly reviewed the supporting data behind these recommendations. As the IPASS trial showed, more patients with EGFR mutation–positive
disease responded to gefitinib than to chemotherapy (71% vs 47%). Conversely, more patients with EGFR mutation–negative disease responded to chemotherapy than to gefitinib (24% vs 1%).

Since the IPASS trial, 6 different trials have been performed asking essentially the same question, noted Dr. Horn: Is there a difference between tyrosine kinase inhibitors (TKIs) such as gefitinib, erlotinib, or afatinib and platinum-based chemotherapy in the first-line treatment of the EGFR-mutation patient population? And from the results of these trials, “There was no surprise that there was an improvement in progression-free survival [PFS] regardless of the TKI used compared with chemotherapy, but no significant difference in overall survival,” recapped Dr. Horn.

However, differences in long-term outcomes by EGFR mutational status were seen in the pooled analysis of the LUX-Lung 3 and LUX-Lung 6 studies.3 The investigators found that although afatinib did not improve overall survival compared with chemotherapy in the entire population of both trials, overall survival was “strikingly” improved with afatinib in those with del19 EGFR mutations (31.7 vs 20.7 months). However, “we did not see this benefit in the L858R group,” remarked Dr. Horn, which actually did better with chemotherapy.

In a recent study from Japan,4 the combination of erlotinib and bevacizumab appeared to offer a PFS advantage over erlotinib alone in patients with EGFR mutation–positive NSCLC (exon 19 deletion and exon 21 L858R mutations). In addition, unlike the LUX studies, patients with both types of EGFR mutations seemed to derive a PFS benefit from the combination treatment in this study, although the overall survival data are not yet mature.

The use of a TKI after disease progression in EGFR mutation–positive NSCLC met with mixed results in 2 recent studies—both presented at the 2014 European Society for Medical Oncology annual meeting. Park et al5 showed that continuing a TKI after first disease progression might provide an additional 3.7 months of benefit. However, Mok et al6 showed no significant improvement in PFS by combining chemotherapy with gefitinib in patients progressing on first-line gefitinib.

“So for patients who are progressing on their first-line TKI, the recommendation is to stop their TKI and start chemotherapy on its own,” stated Dr. Horn.

Third-generation TKIs targeting resistant EGFR mutations, such as AZD9291 and CO-1686, have generated a lot of excitement, with encouraging early data presented at the 2014 ASCO meeting.7,8 In one study, nearly 60% of patients with EGFR T790M-positive mutations showed response to treatment with AZD9291 compared with only 20% of those without this mutation.7 A similar waterfall plot was seen with CO-1686, with a response rate of 58%.8

“What is interesting about these third-generation agents is that unlike with erlotinib and afatinib, there is significantly less rash with AZD9291 and CO-1686,” stated Dr. Horn. The rate of hyperglycemia with CO-1686 is about 16% and is not seen with
AZD9291. “At our institution, I have a very low threshold for initiating metformin if we see elevated blood sugars in patients on clinical trial receiving CO-1686, and it seems to control the hyperglycemia very well,” Dr. Horn suggested.

**Targeting ALK Mutations**

The standard of care in the first-line setting for ALK-positive NSCLC is crizotinib. In fact, the 2015 NCCN Guidelines for NSCLC rank crizotinib as a category 1 option for patients with this gene mutation. Other second-generation ALK inhibitors currently under study are ceritinib, alectinib, and X396, which Dr. Horns indicates may have a better safety profile than ceritinib.

The data behind the ceritinib recommendation were presented by Camidge et al in 2012. Since then, more supporting data from the PROFILE 1007 and 1014 studies have shown that ceritinib is superior to standard chemotherapy in those with previously treated lung cancer with the ALK rearrangement. In addition, “There was an improvement in many quality-of-life scales, including dyspnea, cough, fatigue, and pain control,” Dr. Horn noted.

Ceritinib has been approved for the treatment of ALK-rearranged NSCLC after disease progression on crizotinib. Shaw et al showed that ceritinib was beneficial in this population regardless of the presence of resistance mutations in ALK. Although response rates were similar in patients who had and had not received prior crizotinib (nearly 60%), a slight difference was seen in PFS: those who were crizotinib-naïve had a longer PFS than those who had received this drug already.

“The fact that ceritinib works in the central nervous system is an important factor, given that approximately 50% of patients who are on crizotinib will progress with that as their site of disease,” added Dr. Horn.

**Targeting ROS1 and BRAF Mutations**

Similar to EGFR and ALK, both ROS1 fusions and BRAF mutations do not overlap with other oncogenic driver mutations. ROS1 fusions typically are found in patients with adenocarcinoma who are never/former light smokers. BRAF mutations are found more commonly in patients with adenocarcinoma who are smokers.

Dr. Horn briefly looked at early study data with both crizotinib and the BRAF V600E inhibitor dabrafenib. First, crizotinib appeared to be more effective in ROS1-positive NSCLC than in ALK-positive NSCLC, with an objective response rate of 72% in those with ROS1 fusions and an “impressive” PFS of 19.2 months.

As for dabrafenib, which is an approved option for melanoma, a phase II trial of this agent in patients with NSCLC with the BRAF V600E mutation showed its anticancer activity, with durable objective responses and an acceptable safety profile. This trial has now been expanded to evaluate dabrafenib plus trametinib, an approved combination treatment for patients with melanoma with this type of gene mutation, noted Dr. Horn.

**References**


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