Experts Discuss the Promises and Challenges With Targeted Therapies

Written by Jenny Powers

The initial speaker at the seminar on targeted therapies in non–small cell lung cancer (NSCLC) was Alice T. Shaw, MD, PhD, Massachusetts General Hospital, Boston, Massachusetts, USA. She detailed the rise and partial fall in efficacy seen with tyrosine kinase inhibitors (TKIs) of the anaplastic lymphoma kinase (ALK) pathway. Citing crizotinib as an example, she noted that crizotinib showed stunning results in patients with NSCLC who also had ALK rearrangement; the response rates were 65% (95% CI, 58 to 72) with crizotinib versus 20% (95% CI, 14 to 26) with chemotherapy (p<0.001) [Shaw et al. *N Engl J Med* 2013] until the seemingly inevitable shadow of resistance fell. Targeted therapy is likely to become a continuum of developing novel agents as mutations conferring resistance arise.

At least 27 ALK fusion variants have been reported in lung cancer since the first was described in 2007 [Ou S-H et al. *Oncologist* 2012]. ALK fusion leads to constitutive kinase activation and represents a strong oncogenic driver in lung cancer; ALK-driven cancers are oncogene addicted. Crizotinib is a multitargeted TKI with activity against MET, ALK, and ROS1 [Cui et al. *J Med Chem* 2011]. The latter two drivers have similar domains with 77% identity in the ATP-binding site [Shaw et al. ASCO 2012 Abstract 7508].

In terms of clinical features, both ALK and ROS rearrangement are found equally among men and women and in nonsmokers, and they are drivers of adenocarcinoma. The frequency of ALK and ROS rearrangement in NSCLC is 3% to 7% and 1%, respectively [Soda M et al. *Nature* 2007; Bergethon K et al. *J Clin Oncol* 2012].

Findings from a Phase 3 trial [Shaw AT et al. *N Engl J Med* 2013] showed that patients with ALK-positive NSCLC receiving crizotinib achieved superior progression-free survival (PFS) of a median of 7.7 months compared to 3.0 months with chemotherapy (p<0.001). Crizotinib became and remains the standard first-line therapy in patients with ALK-positive or ROS-positive NSCLC. Acquired resistance to crizotinib has appeared, however, and this has been attributed to mutations in the ALK gene [Lovly C et al. *Sci Trans Med* 2012].

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Several next-generation ALK inhibitors are being investigated in Phase 1, 2, and 3 trials. They have the advantage of being uniformly effective in patients demonstrating crizotinib resistance, regardless of whether a resistance mutation has been identified in the tumor, said Dr. Shaw. Next-generation ALK inhibitors are likely to become standard in the treatment of crizotinib-resistant NSCLC, according to Dr. Shaw. Overall response rates (ORRs) have been confirmed so far only for ceritinib, however. The ORR with ceritinib in a Phase 1 study was 56% (range, 48% to 67%) in 80 patients versus 55% with alectinib in a Phase 1 study with 44 patients and 61% with AP26113 in 31 patients with ALK+ crizotinib-resistant NSCLC [Shaw et al. *N Engl J Med* 2014; Ou *European Cancer Cong.* 2013]. A comparison of ceritinib and these other novel agents is summarized in Table 1.

Dr. Shaw ended her talk by predicting that the next challenge in NSCLC will be to find strategies to counteract the resistance to next-generation inhibitors that will inevitably develop. She commented that combination therapy would likely be a promising approach, and she suggested that ALK and epidermal growth factor receptor (EGFR) inhibitor combinations or ALK inhibitors together with immunotherapy could provide benefit to patients with NSCLC who acquire resistance to crizotinib and next-generation ALK inhibitors.

Caicun Zhou, MD, PhD, Shanghai Pulmonary Hospital, Tongi University, Shanghai, China, reviewed strategies to target the EGFR, which has been identified as the oncogenic driver in 54% of patients with NSCLC [Kris MG et al. ASCO 2011 CRA7501].

Table 1. Comparison of Second-Generation ALK TKIs in Crizotinib-Resistant ALK+ Non–Small Cell Lung Cancer

ALK TKI	Company	Overall Response Rate	Progression-Free Survival	Central Nervous System Activity	Side Effects or Other
Ceritinib (LDK378)	Novartis	56% (45 of 80) confirmed	6.9 months	Yes	Gastrointestinal side effects are common. 750 mg is RP2D and MTD.
Alectinib (RO5424802)	Roche	55% (24 of 44) unconfirmed and confirmed	N/A	Yes	Well tolerated RP2D is 600 mg twice daily, not at MTD
AP26113	Ariad	61% (19 of 31) unconfirmed and confirmed	N/A	Yes	Well tolerated 10–15% early pulmonary toxicity, including gr5

RP2D=recommended Phase 2 dose; MTD=maximum tolerated dose.

Nine Phase 3 trials of the approved EGFR-TKIs (quinazline, gefitinib, erlotinib, and afatinib) for first-line treatment have shown superior PFS, tumor response rate, quality of life, and safety compared with standard chemotherapy (CT) in 1957 patients with NSCLC [Haaland B et al. *J Thorac Oncol* 2014]. Overall survival (OS) was not improved, however. Based on these results, EGFR-TKIs have become standard first-line treatment for advanced NSCLC with positive EGFR mutation; 30% of patients, however, are nonresponders, PFS is 6 to 11 months, and relapses are unavoidable, according to these data.

In the LUX-Lung 6 and 3 trials, patients receiving afatinib achieved PFS of median 11.0 and 11.1 months versus PFS of 5.6 and 6.8 months seen with gemcitabine plus cisplatin or cisplatin plus pemetrexed ($p<0.0001$ and $p=0.0004$) in respective trials [Wu Y et al. *ASCO* 2013; Sequist LV et al. *J Clin Oncol* 2013].

Although there are several modalities for the sequence of CT and EGFR-TKI, it is not known which approach is best. However, in Dr. Zhou's opinion, first-line CT followed by EGFR-TKIs is not better than EGFR-TKI monotherapy.

Next-generation EGFR-TKIs are CO-1686 and AZD 9291, which are active in T790M-mutation-positive patients with NSCLC. These drugs should be less toxic and more potent because they target the wild-type EGFR signaling pathway, said Dr. Zhou, in patients with acquired resistance to TKIs. In the Response Evaluation Criteria in Solid Tumors (RECIST) study, about 67% of patients with T790M-positive NSCLC had a durable tumor response with CO-1686 [Soria JC. WCLC 2013. Abstract 1354]. The toxicity profile was acceptable, with reports of low-grade adverse events (AEs) by only 22% of patients, and no cases of acneiform rash were reported.

Other novel TKIs include dacomitinib, which targets 3 HER receptors and halts disease progression. A trial of dacomitinib versus erlotinib is planned in patients with advanced NSCLC who received no previous systemic therapy.

Dr. Zhou said that although EGFR-TKIs remain the standard first-line therapy in EGFR-mutated NSCLC, encouraging activity has been demonstrated by newer EGFR-TKIs in T790-mutated NSCLC. EGFR antibodies do not appear to be effective for non–squamous cell NSCLC. Dr. Zhou pointed out that afatinib is active in patients with less common mutations. Nevertheless, TKIs given in the second line yield inferior results to second-line chemotherapy across the board in terms of PFS and ORR in patients with wild-type EGFR.

The challenge of targeting new pathways was discussed by Alex A. Adjei, MD, of Roswell Park Cancer Institute, Buffalo, New York, USA. Areas of active research that look promising are the Wnt and Hedgehog pathways. Wnt signaling has been recognized as important in other cancers, especially colorectal cancer, and recently emerged as a pathway crucial to lung carcinogenesis [Stewart D et al. *J Nat Cancer Inst* 2014]. Wnt inhibition has been shown to reduce cell proliferation in NSCLC cell lines [Waaler et al. *Cancer Res* 2012].

Dr. Adjei pointed out that aberrant activation of the Hedgehog signaling pathway has been shown to be associated with malignancy, leading to its being considered a prognostic marker. Inhibition of this pathway has also been shown to increase the sensitivity of NSCLC tumors to treatment.