INTERVIEW

Alice Shaw, MD, PhD

Dr Shaw is Assistant Professor of Medicine at Harvard Medical School in Boston, Massachusetts.

Tracks 1-14

Select Excerpts from the Interview

Tracks 1-2

DR LOVE: What is your practical algorithm for testing for tumor driver mutations in non-small cell lung cancer (NSCLC)?

DR SHAW: In addition to alterations in KRAS, EGFR, ALK and ROS1 genes, a slew of small subsets of lung adenocarcinomas are defined by key oncogenic drivers, against which targeted therapies may be on the horizon. Currently, the NCCN guidelines recommend testing for EGFR and ALK at the time of diagnosis, regardless of smoking history, for patients with nonsquamous NSCLC.

This is important for the appropriate selection of first-line therapy. The NCCN recommendation is for patients with unresectable or advanced NSCLC. Presumably, patients

with resectable disease have undergone curative therapy, either with surgery or definitive radiation therapy. Targeted therapies have no role in that setting.

DR LOVE: What about testing for ROS1 gene rearrangements in terms of treatment decision-making?

DR SHAW: ROS1 is one of the newest targets in NSCLC. Preliminary data indicate that ROS1 represents another good target for crizotinib. Results from the Phase I study of crizotinib for patients with advanced NSCLC harboring ROS1 rearrangements demonstrated a response rate of about 60% (Shaw 2012; [1.1]). The durability of response was as impressive as that in ALK-positive NSCLC. Fewer patients were enrolled because ROS1 rearrangements are rarer than ALK rearrangements. I believe that crizotinib will become a standard therapy for patients with ROS1 rearrangements.

In our institution, we perform up-front testing for the common mutations, EGFR and ALK. If the results are negative, we test for ROS1. Although ROS1 rearrangements are tightly associated with never and light smokers, it is possible for a smoker to have this genetic abnormality. Therefore, regardless of smoking history, if a patient's adenocarcinoma is negative for the more common mutations, we then screen for ROS1 rearrangements.

1.1

Clinical Activity of Crizotinib in Advanced Non-Small Cell Lung Cancer Harboring ROS1 Gene Rearrangements

Best response	n = 14
Overall response rate	57.1%
Complete response	7.1%
Partial response	50%
Stable disease	28.6%
Progressive disease	14.3%

Shaw AT et al. *Proc ASCO* 2012;**Abstract 7508**.

Track 4

DR LOVE: Would you discuss the results of the Phase II SELECT study of adjuvant erlotinib?

DR SHAW: This was a single-arm, multicenter study in which patients with resected EGFR-mutant NSCLC received 2 years of adjuvant erlotinib at the standard dose (Neal 2012; [1.2]).

The expected toxicities of erlotinib were observed, with rash and diarrhea being the most common. The remarkable observation was that the disease-free survival was extremely high at 2 years. This was much higher than expected for such a population of patients with resected tumors. Unfortunately, some patients experienced relapse when erlotinib was discontinued at 2 years. Some of my patients experienced relapse with CNS metastases.

One idea is that patients whose cancer was supposedly completely resected had micrometastatic disease that was kept under control with adjuvant erlotinib. So once treat-

ment was discontinued, the disease progressed. I believe these results are promising. However, a larger, controlled study with longer follow-up is needed to determine the true benefit of adjuvant erlotinib in this setting.

1.2

SELECT: Efficacy and Safety Results of a Multicenter Phase II Trial of Adjuvant Erlotinib in Resected EGFR Mutation-Positive Non-Small Cell Lung Cancer

Efficacy	n = 36	
Two-year disease-free survival	94%	
Adverse events	All grades	Grade 3*
Rash†	89%	17%
Diarrhea†	78%	3%
Fatigue†	61%	6%

* No Grade 4 adverse events reported; † Toxicities leading to dose reductions

Neal JW et al. Multidisciplinary Symposium in Thoracic Oncology 2012;**Abstract 16**.

Tracks 7-8

DR LOVE: Would you talk about some of the clinical trial data that have been reported with crizotinib in ALK-positive NSCLC?

DR SHAW: Recently we reported the results of the Phase III PROFILE 1007 trial, which was the first randomized study of second-line crizotinib versus chemotherapy in ALK-positive NSCLC. All patients received first-line platinum-based chemotherapy, and ALK testing was done using the standard diagnostic FISH assay. Patients received either second-line crizotinib or chemotherapy with pemetrexed or docetaxel.

This was a 1-to-1 randomization in which patients who received chemotherapy were allowed to cross over upon disease progression to receive third-line crizotinib on a separate Phase II study. The primary endpoint of PFS was met, demonstrating that crizotinib is statistically superior to standard chemotherapy, with a PFS of 7.7 months versus 3 months with chemotherapy. We also observed a significant improvement in response rates with a 3-fold increase with crizotinib over chemotherapy.

This was not surprising given what was observed in the Phase I and II trials of crizotinib. No difference in overall survival was observed at the time of final PFS analysis (Shaw 2013b). Because many patients were still receiving treatment at the time, the censoring rate was high. We didn't expect any difference in overall survival because most patients crossed over to receive crizotinib.

One of the most important observations was that crizotinib was associated with significant improvements over chemotherapy in terms of disease-related symptoms, functioning and quality of life. This trial supports the full approval of crizotinib in the United States and was necessary for its approval in other countries, including Europe.

DR LOVE: What is known about the activity of crizotinib in the first-line setting?

DR SHAW: Data on the use of first-line crizotinib in NSCLC are limited. A Phase I trial enrolled 24 patients with untreated, advanced ALK-positive NSCLC. These patients achieved similar response rates — about 60%. The median PFS was 18 months.

The Phase III PROFILE 1014 trial of first-line crizotinib versus platinum/pemetrexed is ongoing and open to accrual (NCT01154140). We hope the target enrollment will be met in about 6 months, soon providing definitive data on the efficacy of first-line crizotinib.

Tracks 10-11

DR LOVE: Would you discuss some of the newer agents being investigated for patients with ALK-positive advanced NSCLC who have developed resistance to crizotinib?

DR SHAW: The second-generation ALK inhibitors are the most exciting agents for patients who have experienced relapse while receiving crizotinib. These oral TKIs — including LDK378, AP26113 and AF802 — are more potent and usually more selective than crizotinib, and in Phase I studies they are already showing promising activity in patients with crizotinib resistance.

LDK378 is the furthest along in clinical development (1.3). This agent is 5 to 10 times more potent and more selective than crizotinib. We already have solid efficacy data, with an overall response rate of approximately 60% for patients with crizotinib-refractory or resistant advanced NSCLC (Shaw 2013a). The duration of response — more than 8 months — is also impressive. So LDK378 seems as though it will be a highly effective salvage treatment once crizotinib is no longer effective. ■

1.3

Editor's Note: FDA Grants Breakthrough Therapy Designation for LDK378 for ALK-Positive Metastatic NSCLC with Progression on or Intolerance to Crizotinib

On March 15, 2013 the investigational compound LDK378 received Breakthrough Therapy designation by the Food and Drug Administration for patients with anaplastic lymphoma kinase-positive metastatic non-small cell lung cancer who experienced disease progression during treatment with, or were intolerant to, crizotinib.

Breakthrough Therapy designation is intended to expedite the development and review of drugs that treat serious or life-threatening conditions if the therapy has demonstrated substantial improvement over an available therapy on at least 1 clinically significant endpoint.

SELECT PUBLICATIONS

Bos M et al. **Complete metabolic response in a patient with repeatedly relapsed non-small cell lung cancer harboring ROS1 gene rearrangement after treatment with crizotinib.** *Lung Cancer* 2013;81(1):142-3.

Camidge DR et al. **Activity and safety of crizotinib in patients with ALK-positive non-small-cell lung cancer: Updated results from a phase 1 study.** *Lancet Oncol* 2012;13(10):1011-9.

Neal JW et al. **The SELECT study: A multicenter Phase II trial of adjuvant erlotinib in resected epidermal growth factor receptor (EGFR) mutation-positive non-small cell lung cancer (NSCLC).** Multidisciplinary Symposium in Thoracic Oncology 2012;**Abstract 16**.

Oxnard GR et al. **New targetable oncogenes in non-small-cell lung cancer.** *J Clin Oncol* 2013;31(8):1097-104.

Shaw AT et al. **Clinical activity of the ALK inhibitor LDK378 in advanced, ALK-positive NSCLC.** *Proc ASCO* 2013a;**Abstract 8010**.

Shaw AT et al. **Crizotinib versus chemotherapy in advanced ALK-positive lung cancer.** *N Engl J Med* 2013b;368(25):2385-94.

Shaw AT, Engelman JA. **ALK in lung cancer: Past, present, and future.** *J Clin Oncol* 2013;31(8):1105-11.