INTERVIEW

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Tracks 1-8

Track 1 Identification of the EML4-ALK fusion oncogene in NSCLC

Track 2 Clinical implications of the IPASS trial results for EGFR mutation testing in clinical practice

Track 3 BIBW 2992 as treatment for patients with EGFR mutations and those resistant to EGFR TKIs

Track 4 Mechanisms of resistance to erlotinib or gefitinib in EGFR-mutant NSCLC

Track 5 **Case discussion:** A 45-year-old woman and never smoker with biopsy-proven recurrent NSCLC who harbors EML4-ALK is enrolled on a clinical trial of the dual ALK/MET inhibitor crizotinib

Track 6 Efficacy, side effects and tolerability of crizotinib

Track 7 Incidence of EML4-ALK in unselected and selected patients with NSCLC

Track 8 Testing for the EGFR mutation and EML4-ALK

Select Excerpts from the Interview

Tracks 1, 5-7

DR LOVE: Would you summarize what we know about EML4-ALK rearrangements in NSCLC?

DR KWAK: Cancer with EML4-ALK rearrangement appears to be independent of cancer with EGFR mutation. In the EGFR-mutant NSCLC population, patients tend to have adenocarcinomas, be women, be of Asian ethnic descent and have a nonsmoking or light smoking history.

Some of those features are also common among patients with ALK rearrangement, in particular the adenocarcinoma histology and the light smoking or nonsmoking history. However, if you examine the gene status of a group of patients chosen phenotypically for those features, you'll find that EGFR mutation, ALK gene rearrangement and K-ras mutation are mutually exclusive in NSCLC (Shaw 2009).

DR LOVE: Would you discuss a patient you treated with the EML4-ALK inhibitor crizotinib (PF-02341066) on a clinical trial?

DR KWAK: I had a 45-year-old patient with no history of smoking who presented with a cough and hemoptysis. A CT scan revealed a 4-cm opacity in the left lower lobe, and biopsy confirmed an adenocarcinoma. She underwent a lobectomy that revealed 21 negative nodes, and she received adjuvant chemotherapy for Stage T2N0M0 NSCLC with wild-type EGFR.

About a year and a half later she developed recurrent disease and began receiving erlotinib. However, within two months of beginning erlotinib treatment, our lab tested her tumor and found ALK rearrangement. She was enrolled on the crizotinib trial and experienced a remarkable response. Prior to receiving this agent, CT had shown a diffuse distribution of tumor across the left side of her lung. At the first restaging, only two months after starting treatment, no disease was visible on a CT scan and she felt well.

Seventeen months later she's still on the trial. She's hiking, doing the things she likes to do and has a high quality of life. It's been rewarding to see patients such as this fare so well on this drug.

DR LOVE: Would you describe how the drug is administered and its tolerability?

DR KWAK: It's an oral drug that's currently administered twice a day at 250 mg. The most common side effects have been mild nausea and some vomiting, some of which can be modified with the intake of a small amount of food (Bang 2010). Other side effects we've seen include lower-extremity edema, fatigue and some visual symptoms. The visual disturbances are described as trails of light that follow objects, especially when people are waking up in the morning or during transitions from dark to light or light to dark.

Some of these patients are experiencing so many symptoms when they join the trial that, despite these side effects, they feel much better overall on the drug because of the improvement in their disease status, and the side effects of the drug seem relatively minor.

We've had some patients develop elevations of alanine transaminase, and in a few patients these increases have been dose limiting. For some, rechallenging with a lower dose can successfully keep the patient on the drug while minimizing the effects on liver function. All the elevated liver function test results have been reversible on withdrawal of the drug.

DR LOVE: What have you seen with regard to efficacy?

DR KWAK: The trial is ongoing so the number of patients receiving the treatment continues to increase, but as of December 2009 approximately 64 patients had received the drug and 50 of them were evaluable for response. At that time the objective response rate was 64 percent and 90 percent of patients had experienced either stable disease or response (Bang 2010; [3.1]). We find that notably few patients experience no response to the drug.

DR LOVE: What proportion of patients with NSCLC do you estimate have the ALK fusion gene, and what are the clinical implications?

3.1

Activity of Crizotinib in a Phase I Study for Patients with ALK-Positive Non-Small Cell Lung Cancer (N = 82)

Parameter		Outcome
Objective response rate (ORR)		57%
Number of prior regimens[1] and ORR	0	80%
	1	52%
	2	67%
	≥3	56%
Disease control rate (DCR) at eight weeks*		87%
Six-month progression-free survival probability[2]		72%

Toxicity: The most frequent adverse events were mild and moderate gastrointestinal events, including nausea (54%) and vomiting (44%), and mild visual disturbances (42%).

* DCR = complete responses + partial responses + stable disease at eight weeks
[1] Unknown for one patient; [2] Median follow-up for progression-free survival: 6.4 months

Bang Y et al. *Proc ASCO* 2010;**Abstract 3**.

DR KWAK: In an unselected NSCLC population, various groups have reported from a little more than one percent to as much as seven percent. Alice Shaw has described a 13 percent incidence of ALK fusion genes in a selected group of patients, particularly those with light smoking or nonsmoking histories and adenocarcinoma histology. In addition, if you exclude patients with EGFR mutations from that group, I believe that the incidence of ALK fusion genes could be as high as 33 percent in nonsmokers.

So if we analyze the genes that seem most likely to be abnormal within this demographically selected population, then I believe it's possible to prospectively identify these patients and administer appropriate therapy.

Although the majority of patients with this gene have light smoking or nonsmoking histories and adenocarcinoma histology, exceptions exist. For example, a few of our patients with ALK positivity had longer than 10-pack-year smoking histories, and although adenocarcinoma is by far the most common histology, one can encounter cases in which the histology is somewhat unclear.

So I believe that if one suspects EML4-ALK positivity, particularly in young patients because that tends to be one of the demographic features, then it's worth testing the tumor. ■

SELECT PUBLICATIONS

Bang Y et al. **Clinical activity of the oral ALK inhibitor PF-02341066 in ALK-positive patients with non-small cell lung cancer (NSCLC).** *Proc ASCO* 2010;**Abstract 3**.

Shaw AT et al. **Clinical features and outcome of patients with non–small-cell lung cancer who harbor EML4-ALK.** *J Clin Oncol* 2009;27(26):4247-53.

Soda M et al. **Identification of the transforming EML4-ALK fusion gene in non-small-cell lung cancer.** *Nature* 2007;448(7153):561-6.