



INTERVIEW

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Tracks 1-14

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- Track 2** **Case discussion:** A 62-year-old patient and former smoker with advanced, EGFR-mutant NSCLC experiences disease progression after 10 months of response to erlotinib
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- Track 14** **Case discussion:** A 41-year-old patient and former moderate smoker with recurrent, pan-wild-type adenocarcinoma less than 1 year after completing definitive chemoradiation therapy for Stage IIIB NSCLC

Select Excerpts from the Interview

Track 6

- ▶ **DR LOVE:** Would you discuss the mechanism of action of various EGFR tyrosine kinase inhibitors (TKIs)?
- ▶ **DR SEQUIST:** There are 3 generations of EGFR TKIs. Gefitinib and erlotinib are first-generation, reversible TKIs that compete for receptor-binding with ATP. I explain to my patients that both of these TKIs bind tightly to EGFR like a strong magnet, but the binding is not permanent. If one pulls hard enough, the connection can be dissociated.

The second-generation TKIs, like afatinib and dacomitinib, covalently bind, irreversibly, to the ATP-binding site of the receptor. Afatinib and dacomitinib are both pan-HER inhibitors with strong binding affinities for both HER2 and EGFR. In laboratory experiments, second-generation TKIs can overcome the EGFR T790M mutation, the most common acquired secondary EGFR mutation. Several clinical studies are ongoing to provide definitive answers about whether this effect applies in patients.

In general, the degree of activity of the second-generation TKIs in patients with erlotinib-resistant NSCLC has been somewhat disheartening. Because of the strong covalent binding nature of these TKIs, some of the side effects can prohibit the administration of the required dose needed to prevent or overcome the EGFR T790M mutation. With these agents, patients seem to develop more rash and diarrhea than with the first-generation TKIs. They are effective in treatment-naïve NSCLC but not quite as efficacious for patients with drug-resistant disease.

A third generation of TKIs is currently being clinically investigated. The difference is that these agents do not block wild-type EGFR. They do not cause rash or diarrhea because they do not inhibit EGFR in noncancerous cells. Rather, they target EGFR-activating mutations like T790M. Many third-generation TKIs are currently in Phase I clinical trials. It will be exciting to see the results from these studies in the coming years.

 **Track 7**

▶ **DR LOVE:** Would you discuss the results of the Phase III LUX-Lung 3 trial?

▶ **DR SEQUIST:** The LUX-Lung 3 trial evaluated afatinib versus cisplatin/pemetrexed as first-line therapy for patients with advanced EGFR-mutant NSCLC (Sequist 2013; [2.1]). It's the first trial to compare second- or third-generation TKIs to a pemetrexed-based regimen. Pemetrexed has evolved into one of our favorite agents, at least in the United States, for patients with lung adenocarcinoma. So a randomized trial of an EGFR TKI versus a pemetrexed-based chemotherapeutic regimen was needed.

Patients received 6 cycles of cisplatin/pemetrexed or daily afatinib. PFS and quality of life were significantly improved with afatinib. The majority of patients on the trial had NSCLC harboring EGFR mutations with exon 19 deletion or L858R mutation. Approximately 11% of patients on the trial had atypical mutations that are less responsive to EGFR TKIs.

2.1 LUX-Lung 3: A Phase III Trial Evaluating Afatinib versus Cisplatin/Pemetrexed (Cis/Pem) as First-Line Therapy for Advanced EGFR-Mutant Non-Small Cell Lung Cancer

Efficacy	Afatinib (n = 230)	Cis/pem (n = 115)	Hazard ratio	p-value
Median PFS: All patients	11.1 mo	6.9 mo	0.58	<0.001
Median PFS: Patients with del(19)/L858R	13.6 mo	6.9 mo	0.47	<0.001
Objective response rate	56.1%	22.6%	—	0.001
Median duration of response	11.1 mo	5.5 mo	—	—

PFS = progression-free survival

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In the entire study population, the median PFS was approximately 11 months with afatinib. A subgroup analysis of patients with the classical EGFR mutations demonstrated a median PFS of 13.6 months with first-line afatinib. If these results are compared across trials to the observations in the IPASS trial of gefitinib (Mok 2009) or the EURTAC trial, which resulted in a median PFS of 9.7 months with erlotinib (Rosell 2012), it appears that second-generation TKIs such as afatinib may yield a longer median PFS by an average of 2 to 4 months. However, the first- and second-generation TKIs have yet to be compared head to head.

Tracks 9-10

► **DR LOVE:** Based on the preliminary results of the Phase II SELECT trial, what is your perspective on the current role of adjuvant TKI therapy in NSCLC (Neal 2012)?

► **DR SEQUIST:** The single-arm SELECT trial evaluated 100 patients with resected, EGFR-mutant NSCLC who received adjuvant erlotinib for 2 years. The study is ongoing, and the mature results are not yet available. At ASCO 2012 we presented the fairly mature data for the first 36 patients enrolled on the study. It took several years to accrue 100 patients. By the time the hundredth patient was enrolled, the first 36 patients had been followed for a good amount of time.

Analysis of results for the first 36 patients reported a low rate of disease progression during treatment. Only 1 patient in that group experienced disease progression while receiving adjuvant erlotinib. A handful of patients experienced progressive disease within 6 months of discontinuing therapy.

This observation may be reflected in the mature data from 100 patients, demonstrating that this strategy is not curative but instead delays the appearance or emergence of metastatic disease.

When you consider patients with advanced disease and you see the response rate with chemotherapy in the neighborhood of 30% and the response rate with TKIs in the neighborhood of 75%, it seems obvious that if chemotherapy helps in the adjuvant setting, an EGFR TKI should help more. But many concepts in medicine seem obvious until you test them. In order to know whether a small group of patients exists whom you are moving from recurrence to cure, you need a randomized study. So together with the NCI, CALGB is now working on a randomized trial in which patients would receive either placebo or erlotinib. In addition, we are opening another trial at Mass General, Memorial Sloan-Kettering and Stanford University evaluating adjuvant afatinib for patients with fully resected EGFR-mutant tumors. ■

SELECT PUBLICATIONS

Mok TS et al. **Gefitinib or carboplatin-paclitaxel in pulmonary adenocarcinoma.** *N Engl J Med* 2009;361(10):947-57.

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.**

Rosell R et al. **Erlotinib versus standard chemotherapy as first-line treatment for European patients with advanced EGFR mutation-positive non-small-cell lung cancer (EURTAC): A multicentre, open-label, randomised phase 3 trial.** *Lancet Oncol* 2012;3(3):239-46.

Sequist LV et al. **Phase III study of afatinib or cisplatin plus pemetrexed in patients with metastatic lung adenocarcinoma with EGFR mutations.** *J Clin Oncol* 2013;[Epub ahead of print].