INTERVIEW

Lecia V Sequist, MD, MPH

Dr Sequist is Associate Professor of Medicine at Harvard Medical School in Boston, Massachusetts.

Tracks 1-11

Track 1 **Case discussion:** A 44-year-old woman and never smoker with advanced T790M-mutant adenocarcinoma of the lung experiences a very good partial response to rociletinib (CO-1686) on a clinical trial after disease progression on erlotinib

Track 2 Afatinib as first-line therapy for patients with advanced EGFR-mutant non-small cell lung cancer (NSCLC)

Track 3 Role of afatinib/cetuximab in advanced EGFR-mutant NSCLC after disease progression on erlotinib

Track 4 Activity of afatinib versus erlotinib in common EGFR-activating mutations

Track 5 Therapeutic options for patients with recurrent EGFR-mutant adenocarcinoma without the T790M resistance mutation

Track 6 Response and tolerability of the third-generation EGFR TKIs rociletinib and osimertinib (AZD9291)

Track 7 Investigation of third-generation EGFR TKIs as first-line therapy for advanced EGFR mutation-positive NSCLC

Track 8 **Case discussion:** A 44-year-old woman and never smoker with Stage IIIA EGFR mutation-positive adenocarcinoma of the lung enrolls on the SELECT trial and receives 2 years of adjuvant erlotinib

Track 9 Results of the SELECT study: A multicenter Phase II trial of adjuvant erlotinib in resected EGFR-mutant NSCLC

Track 10 Reconciling the SELECT and RADIANT study results with adjuvant erlotinib

Track 11 Targeting uncommon mutations (eg, HER2, BRAF) as actionable drivers in lung cancer

Select Excerpts from the Interview

Tracks 1-3, 6-7

CASE DISCUSSION: A 44-year-old woman and never smoker with previously treated Stage IV T790M-mutant adenocarcinoma of the lung experiences a very good partial response to a third-generation EGFR tyrosine kinase inhibitor (TKI) on a clinical trial

DR SEQUIST: The patient was a healthy, athletic mother of 4 who worked in a school and was having trouble breathing. She was seen at another center and found to have Stage IV EGFR exon 19 mutation-positive adenocarcinoma with bilateral pulmonary nodules and an adrenal metastasis. She achieved a quick response to first-line erlotinib, which was maintained for about 10 months. When her breathing started to worsen, she received afatinib for 2 months without any response.

The choice to administer afatinib after erlotinib is not evidence based. People believe that the newer drug should be used after the older one, but the data suggest that

afatinib can be a good first-line EGFR inhibitor. Once a patient has received either erlotinib or afatinib in the first line, I don't believe we gain much by switching to the other. The Phase IIb/III LUX-Lung 1 trial evaluated afatinib or placebo for patients who had previously received chemotherapy and a first-generation EGFR inhibitor, either erlotinib or gefitinib. No overall survival benefit was reported, the primary endpoint, and only 7% of the patients achieved a partial response on the afatinib arm (Miller 2012).

After the 2 months of afatinib, the patient was referred to me and received rociletinib on a clinical trial. She achieved a dramatic partial response on her first scan, and this has been maintained for about 10 months. However, she experienced hyperglycemia that is being well managed with metformin.

DR LOVE: What are your thoughts on the efficacy of the third-generation EGFR TKIs rociletinib and osimertinib (AZD9291) in the treatment of non-small cell lung cancer (NSCLC)?

DR SEQUIST: Both agents seem to be active in Phase I and Phase II studies, especially in patients with T790M mutations (1.1; 1.2). They are designed to hit both the activating mutations and the T790M EGFR mutations but not the wild-type form. Inhibition of wild-type EGFR causes the rash, diarrhea and nail changes observed with the older-generation inhibitors. The hyperglycemia associated with rociletinib in some patients can be managed with metformin. The response rate for both osimertinib and

1.1

AURA: A Phase I/II Trial of Osimertinib (AZD9291) for Patients with EGFR Mutation-Positive Locally Advanced or Metastatic Non-Small Cell Lung Cancer

	Dose-escalation and expansion cohorts[1]			First-line cohort[2]
Response	**All patients** (n = 239)	**T790M-positive** (n = 127)	**T790M-negative** (n = 61)	**All patients** (n = 60)
ORR (evaluable)	51%	61%	21%	73%
DCR (evaluable)	84%	95%	61%	97%
Survival	**n = 222**	**n = 138**	**n = 62**	**n = 60**
Median PFS	8.2 months	9.6 months	2.8 months	Not reached

ORR = objective response rate; DCR = disease control rate; PFS = progression-free survival

[1] Jänne PA et al. *N Engl J Med* 2015;372(18):1689-99; [2] Ramalingam SS et al. *Proc ASCO* 2015;**Abstract 8000**.

1.2

Results of a Phase I/II Trial of Rociletinib (CO-1686) for Patients with EGFR Mutation-Positive Non-Small Cell Lung Cancer After Failure of an EGFR Inhibitor

Outcome (any dose)	**T790M-positive** (n = 46)	**T790M-negative** (n = 17)
ORR	59%	29%
DCR	93%	59%
Median PFS	13.1 months	5.6 months

ORR = objective response rate; DCR = disease control rate; PFS = progression-free survival

Sequist LV et al. *N Engl J Med* 2015;372(18):1700-9.

rociletinib is approximately 60% for patients with T790M-mutant disease (1.1; 1.2). I've administered osimertinib to several patients, and most have not experienced any side effects.

The ongoing Phase II/III TIGER-1 trial is investigating rociletinib versus erlotinib as first-line therapy for patients with EGFR mutation-positive advanced NSCLC (NCT02186301). Also, the ongoing Phase III FLAURA trial is assessing osimertinib versus erlotinib or gefitinib as first-line therapy for patients with EGFR-mutant advanced NSCLC (NCT02296125). I believe these agents will have a huge effect for patients when they're FDA approved.

Editor's note: Subsequent to this interview, on November 13, 2015, the FDA granted accelerated approval to osimertinib for patients with advanced EGFR T790M mutation-positive NSCLC after disease progression on a prior EGFR TKI.

DR LOVE: Do you see a role for afatinib/cetuximab in the treatment of advanced NSCLC?

DR SEQUIST: I would use this combination in the right situation, as it has a track record of activity. Afatinib alone is not active after acquired resistance to EGFR inhibitors, but when used in combination with cetuximab, a consistent response rate of 30% has been observed in a couple of different populations (Janjigian 2014). The caveat is that this combination can cause a significant amount of dermatologic toxicity.

The ongoing Phase II/III SWOG-S1403 trial is evaluating afatinib with or without cetuximab for patients with newly diagnosed advanced EGFR mutation-positive NSCLC (1.3). The hypothesis is that first-line use of the combination can yield a longer progression-free survival (PFS) versus single-agent afatinib.

1.3

SWOG-S1403: A Phase II/III Trial of Afatinib with or without Cetuximab in Treatment-Naïve Advanced EGFR-Mutant Non-Small Cell Lung Cancer (NSCLC)

Protocol ID: NCT02438722

Target accrual (N = 605)

- Newly diagnosed Stage IV or recurrent NSCLC
- EGFR mutation-positive disease
- Availability of tissue sample
- ECOG PS 0-2

R

- Afatinib
- Afatinib + cetuximab

Primary endpoint: Progression-free survival (Phase II); overall survival (Phase III)

www.clinicaltrials.gov. Accessed December 2015.

Tracks 9-10

DR LOVE: Would you discuss the design and results of the Phase II SELECT trial and the Phase III RADIANT trial of adjuvant erlotinib for patients with Stage I to Stage III NSCLC?

DR SEQUIST: The main issue with the SELECT trial design is that it was a single-arm study, so it is difficult to draw conclusions (Pennell 2014). One hundred patients enrolled on the trial, and all had EGFR mutation-positive disease. Patients received 2

years of adjuvant erlotinib. The trial data are mature and will soon be published. The 2-year disease-free survival (DFS) rate was 96%. So the number of patients with recurrent disease on treatment was low. Now that the patients have stopped the 2 years of adjuvant erlotinib, we've started to see more disease recurrence.

RADIANT was a prospective randomized trial that was not limited to patients with EGFR-mutant disease. However, a small proportion of patients had EGFR mutation-positive disease. Patients were randomly assigned to 2 years of adjuvant erlotinib versus placebo (Kelly 2015; [1.4]).

In the overall population of patients, the study demonstrated no significant difference in DFS. Because of the hierarchical testing procedure, if the overall analysis was negative, the investigators had no option to evaluate statistical significance in any of the patient subgroups. Even though the *p*-value was 0.039 for patients with EGFR mutation-positive disease, it did not translate to a statistically significant DFS advantage.

Hopefully, the ongoing randomized ALCHEMIST trial of erlotinib versus placebo will help shed more light on the appropriate treatment approach in terms of adjuvant therapy for patients with completely resected EGFR mutation-positive disease (NCT02193282). ■

1.4

RADIANT: Efficacy and Safety Results of a Phase III Trial of Adjuvant Erlotinib versus Placebo for Patients with Stage IB to IIIA Non-Small Cell Lung Cancer

Median DFS	Erlotinib	Placebo	Hazard ratio	*p*-value
All patients (n = 623, 350)	50.5 mo	48.2 mo	0.9	0.324
EGFR-mutant population (n = 102, 59)	46.4 mo	28.5 mo	0.61	0.039*
	Erlotinib (n = 611)		Placebo (n = 343)	
Select adverse events	All	Grade ≥3	All	Grade ≥3
Rash	86.4%	22.3%	32.1%	0.3%
Diarrhea	52.2%	6.2%	15.7%	0.3%
Pruritus	26.4%	1.3%	14.9%	0%
Fatigue	19.5%	0.8%	14.3%	0.9%
Dyspnea	14.6%	1.1%	18.1%	1.5%
Anorexia	13.1%	0.7%	7.0%	0.6%

* Not statistically significant because of the hierarchical testing procedure

Kelly K et al. *J Clin Oncol* 2015;33(34):4007-14.

SELECT PUBLICATIONS

Janjigian YY et al. **Dual inhibition of EGFR with afatinib and cetuximab in kinase inhibitor-resistant EGFR-mutant lung cancer with and without T790M mutations.** *Cancer Discov* 2014;4(9):1036-45.

Kelly K et al. **Adjuvant erlotinib versus placebo in patients with stage IB-IIIA non-small-cell lung Cancer (RADIANT): A randomized, double-blind, phase III trial.** *J Clin Oncol* 2015;33(34):4007-14.

Miller VA et al. **Afatinib versus placebo for patients with advanced, metastatic non-small-cell lung cancer after failure of erlotinib, gefitinib, or both, and one or two lines of chemotherapy (LUX-Lung 1): A phase 2b/3 randomised trial.** *Lancet Oncol* 2012;13(5):528-38.

Pennell NA et al. **SELECT: A multicenter phase II trial of adjuvant erlotinib in resected early-stage EGFR mutation-positive NSCLC.** *Proc ASCO* 2014;**Abstract 7514**.