INTERVIEW

Lecia V Sequist, MD, MPH

Dr Sequist is Assistant Professor of Medicine at Harvard Medical School and is a medical oncologist at the Center for Thoracic Cancers at Massachusetts General Hospital Cancer Center in Boston, Massachusetts.

Tracks 1-18

Track 1 Activity and tolerability of crizotinib in patients with NSCLC and the EML4-ALK fusion oncogene

Track 2 Assessment of EML4-ALK in clinical practice

Track 3 Erlotinib with the c-Met inhibitor ARQ 197 in advanced K-ras-mutant NSCLC

Track 4 Development of a clinical assay to rapidly perform targeted mutational analysis

Track 5 Tolerability and efficacy of *nab* paclitaxel/carboplatin as first-line therapy for advanced NSCLC

Track 6 CAN-NCIC-BR19: Results of a Phase III study of adjuvant gefitinib in Stage IB to IIIA NSCLC

Track 7 Efficacy, toxicity and quality of life with first-line EGFR TKIs versus chemotherapy for advanced EGFR-mutant NSCLC

Track 8 Mechanisms of resistance to EGFR TKIs and the potential role of irreversible TKIs

Track 9 LUX-Lung 1: A Phase IIb/III study of BIBW 2992 for patients with NSCLC who experience relapse after one or two lines of chemotherapy and erlotinib or gefitinib

Track 10 LUX-Lung 3: A Phase III study of BIBW 2992 versus chemotherapy as first-line treatment for patients with Stage IIIB or IV NSCLC harboring EGFR mutations

Track 11 LUX-Lung 2: BIBW 2992 for patients with adenocarcinoma of the lung and EGFR mutations

Track 12 **Case discussion:** A 39-year-old woman and never smoker presents with an EGFR-mutant adenocarcinoma of the lung and multiple bone and central nervous system (CNS) metastases

Track 13 Efficacy of EGFR TKIs in patients with CNS metastases from EGFR-mutant NSCLC

Track 14 **Case discussion:** A 55-year-old man who is a smoker with cardiac disease and a prior pulmonary embolism is diagnosed with a Stage IV adenocarcinoma of the lung and achieves a near-complete response to six cycles of carboplatin/paclitaxel

Track 15 Lessons learned from a Gyneco-logic Oncology Group ovarian cancer trial: Role of maintenance bevacizumab after carboplatin/paclitaxel/bevacizumab

Track 16 **Case discussion:** An 86-year-old woman with resected Stage II lung cancer undergoes interventional radiation therapy with cement augmentation for a pathologic fracture of the acetabulum

Track 17 Treatment of advanced NSCLC in elderly patients: Single-agent versus platinum-based combination chemotherapy

Track 18 Effect of early palliative care on quality of life and survival in Stage IV NSCLC

Select Excerpts from the Interview

Track 6

DR LOVE: What are your thoughts on the BR19 trial results of adjuvant gefitinib for patients with Stage IB to IIIA NSCLC that were presented at ASCO this year?

DR SEQUIST: This study by NCI Canada was closed early in April 2005. At ASCO 2010, results after several years of follow-up were presented. No survival benefit was reported among patients who received adjuvant gefitinib versus placebo (Goss 2010). Of most concern with these data was the trend toward possible harm from gefitinib, which was observed to be consistent across different subgroups, including those with EGFR mutations. It's not clear what might cause this apparent detriment.

The number of patients who actually received gefitinib and for what period of time before accrual was halted was not reported. I am not sure what to make of these data, mainly because it wasn't clear how much gefitinib patients received or what might have caused the added toxicity. Although concern remains about using an EGFR TKI in the adjuvant setting, I believe that we still have many questions to answer.

DR LOVE: What ongoing trials are addressing this issue?

DR SEQUIST: I am chairing a Phase II single-arm clinical trial for patients with resected, early-stage NSCLC and EGFR mutations who have the option of chemotherapy and then afterward receive two years of erlotinib (NCT00567359). Also, we are awaiting the results of the RADIANT trial, which is evaluating adjuvant erlotinib versus placebo, but instead of taking "all comers," it requires patients to be positive for EGFR overexpression by either immunohistochemistry or FISH. We hope that in two years we will have an answer, and I am especially interested to see the results among patients with EGFR mutations.

Track 7

DR LOVE: What is your first-line approach for a patient with an EGFR mutation and metastatic disease, considering the recent report from the IPASS study?

DR SEQUIST: The use of an EGFR TKI as first-line therapy for patients with advanced, EGFR-mutant NSCLC is becoming the standard. How this approach affects survival is a topic of much discussion. The survival analysis of the IPASS data is not yet mature, but the progression-free survival curves were impressive as were the better quality-of-life data for patients with EGFR mutations whose disease was treated with gefitinib compared to carboplatin/paclitaxel (Mok 2009; [1.1, page 4]). I believe it to be reassuring for patients

who, even if they don't receive gefitinib in the first-line setting, are likely to gain a similar benefit by receiving gefitinib in the second-line setting.

Tracks 8-11

DR LOVE: What is known about mechanisms of resistance to erlotinib or gefitinib, and do the irreversible EGFR TKIs have a role for those patients?

DR SEQUIST: We know that EGFR TKIs work well for patients with EGFR mutations, but they don't cure the cancer. Most, if not all, patients will develop resistance after an average of 10 to 12 months. More and more major cancer centers have been making an effort to perform biopsies when these patients develop resistance to EGFR TKI therapy to learn more about the mechanisms of resistance.

Two main mechanisms of resistance that have been identified are the T790M mutation and MET amplification. T790M occurs in approximately 50 percent of patients and is another mutation in the EGFR that makes it more difficult for a drug such as gefitinib or erlotinib to bind to the receptor and inhibit it. MET is a parallel pathway to EGFR that gets turned up or amplified to compensate for the blocked EGFR signal. Several drugs in development focus on both of these mechanisms of EGFR TKI resistance.

One such drug is the irreversible dual HER2 and EGFR blocker BIBW 2992. We are awaiting results of the recently completed LUX-Lung 1 study, which randomly assigned patients who developed resistance to EGFR TKIs to BIBW 2992 or placebo.

BIBW 2992 is also being evaluated versus cisplatin/pemetrexed in the front-line setting in the LUX-Lung 3 study, which is enrolling patients in the United States and internationally. This is an important study because chemotherapy has evolved in the period since the IPASS study was developed. Pemetrexed has become a foundation of treatment, especially for patients with adenocarcinoma. So the LUX-Lung 3 study of BIBW 2992 versus cisplatin/pemetrexed is probably a more valid, modern chemotherapy comparison.

DR LOVE: What results have been reported to date with BIBW 2992?

DR SEQUIST: James Yang presented data from the LUX-Lung 2 trial at ASCO 2010, which evaluated BIBW 2992 in patients with TKI-naïve disease and EGFR mutations, and the results were good — a high response rate of approximately 60 percent and time to disease progression of more than one year (Yang 2010; [2.1]).

I believe that the irreversible EGFR TKIs are comparable to the first generation when it comes to patients with TKI-naïve disease. The question is, can they combat resistance?

2.1

LUX-Lung 2 Trial: Efficacy and Best Confirmed Response with BIBW 2992 According to RECIST and Type of EGFR Mutation in Patients with Adenocarcinoma

Survival	First-line therapy	Second-line therapy
Median progression-free survival	14.7 mo	11.8 mo
Median overall survival	NA	23.9 mo

Response*	EGFR mutation type		
	Del 19 + L858R (n = 106)	Other (n = 23)	All (n = 129)
Complete response + partial response	64%	43%	60%
Disease control rate	88%	78%	86%
Progressive disease	6%	13%	7%

* Investigator assessment

Yang C et al. *Proc ASCO* 2010;**Abstract 7521**.

Track 15

DR LOVE: How do you approach the use of bevacizumab in NSCLC?

DR SEQUIST: I try to assess every patient with advanced disease in terms of potentially receiving bevacizumab. The lung community is more hesitant about some of bevacizumab's relative contraindications than is the colon cancer community. One important emerging issue is duration of bevacizumab treatment.

An interesting data set reported at ASCO 2010 in ovarian cancer addressed the role of maintenance bevacizumab after chemotherapy. The ECOG-E4599 study, which established the use of bevacizumab in lung cancer, did not address that issue.

2.2

Maintenance Bevacizumab After Carboplatin/Paclitaxel/Bevacizumab for Patients with Advanced Ovarian Cancer

	Arm I CP (n = 625)	Arm II CP + Bev (n = 625)	Arm III CP + Bev → Bev (n = 623)
Patients with event (%)	67.7	66.9	57.8
Median progression-free survival	10.3 mo	11.2 mo	14.1 mo
Hazard ratio	Reference	0.908	0.717
One-sided *p*-value	Reference	0.080	<0.0001

CP = carboplatin/paclitaxel; Bev = bevacizumab

Burger RA et al. *Proc ASCO* 2010;**Abstract LBA1**.

The Gynecologic Oncology Group trial presented at ASCO evaluated carboplatin/paclitaxel versus carboplatin/paclitaxel/bevacizumab with maintenance bevacizumab versus carboplatin/paclitaxel/bevacizumab without maintenance bevacizumab. The authors reported that bevacizumab maintenance provided a significant benefit (Burger 2010; [2.2]).

Track 18

DR LOVE: What are your thoughts on the presentation by Dr Jennifer Temel at ASCO 2010 on the effect of early palliative care in advanced NSCLC?

DR SEQUIST: Dr Temel hypothesized that integrating palliative care when patients begin receiving chemotherapy for advanced NSCLC might improve quality of life for patients with metastatic lung cancer, which was demonstrated in this study.

However, the real buzz was the improvement in survival, despite the fact that patients on both arms received an equal number of chemotherapy regimens and the palliative care group received less aggressive care at end of life (Temel 2010). The Kaplan-Meier curves appeared similar to what was observed in the ECOG-E4599 study, which evaluated carboplatin/paclitaxel with or without bevacizumab (Sandler 2006).

A couple of factors may have contributed to the improvement in survival, including better treatment of depression, which we know occurs at a high rate in lung cancer and is associated with shorter survival. Additionally, better symptom control and faster recognition and treatment of problems may have played a role.

In the end we can't say what contributed to the survival improvement, but Dr Temel is planning a larger, more definitive study to determine whether these results can be replicated in a multicenter fashion. ■

SELECT PUBLICATIONS

Burger RA et al. **Phase III trial of bevacizumab (BEV) in the primary treatment of advanced epithelial ovarian cancer (EOC), primary peritoneal cancer (PPC), or fallopian tube cancer (FTC): A Gynecologic Oncology Group study.** *Proc ASCO* 2010;**Abstract LBA1**.

Goss GD et al. **A phase III randomized, double-blind, placebo-controlled trial of the epidermal growth factor receptor inhibitor gefitinib in completely resected stage IB-IIIA non-small cell lung cancer (NSCLC): NCIC CTG BR.19.** *Proc ASCO* 2010;**Abstract LBA7005**.

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

Sandler A et al. **Paclitaxel-carboplatin alone or with bevacizumab for non-small-cell lung cancer.** *N Engl J Med* 2006;355(24):2542-50.

Temel JS et al. **Effect of early palliative care (PC) on quality of life (QOL), aggressive care at the end-of-life (EOL), and survival in stage IV NSCLC patients: Results of a phase III randomized trial.** *Proc ASCO* 2010;**Abstract 7509**.

Yang C et al. **Phase II study of BIBW 2992 in patients with adenocarcinoma of the lung and activating EGFR mutations (LUX-Lung 2).** *Proc ASCO* 2010;**Abstract 7521**.