INTERVIEW

Corey J Langer, MD

Dr Langer is Professor of Medicine at the University of Pennsylvania and Vice Chair for the Radiation Therapy Oncology Group in Philadelphia, Pennsylvania.

Tracks 1-13

Select Excerpts from the Interview

Track 1

DR LOVE: Would you comment on your trial evaluating the safety of bevacizumab in patients with brain metastases?

DR LANGER: The Phase II/III trial ECOG-E4599, which evaluated carboplatin/paclitaxel with or without bevacizumab, excluded patients with brain metastases, but that exclusion was orchestrated out of fear. No instances of intracranial bleeding occurred in the original Phase I efforts. In the E4599

trial, some of the patients experienced central nervous system (CNS) progression, but no untoward incidents of CNS hemorrhage occurred in that group.

Probably 15 to 25 percent of patients who present with de novo Stage IV NSCLC have brain metastases. Our study addressed whether bevacizumab could be combined safely with first- or second-line therapy for patients with advanced NSCLC and treated brain metastases.

The bottom line is that with more than 100 patients enrolled in our trial, no unexpected safety signals were noted (Socinski 2009; [1.1]). One episode of bleeding occurred prior to the data cut, and that was probably unrelated to the bevacizumab. As a result of this trial and others, the indication for bevacizumab has expanded to include patients with treated brain metastases.

1.1

Safety of Bevacizumab Combined with Chemotherapy for Patients with NSCLC and Brain Metastases

Adverse events	Total (n = 106)	Carboplatin + paclitaxel (n = 37)	Carboplatin + other (n = 30)	Pemetrexed (n = 19)	Erlotinib (n = 11)	Other (n = 9)
CNS hemorrhage (Grade II+)	0	0	0	0	0	0
Pulmonary hemorrhage (Grade III+)	3	1	1	0	1	0
Non-CNS/nonpulmonary hemorrhage (Grade III+)	2	0	2	0	0	0
Arterial thromboembolic events (any grade)	0	0	0	0	0	0
New or exacerbated hypertension (Grade III+)	3	1	0	1	0	1

Socinski MA et al. *J Clin Oncol* 2009;27(31):5255-61.

Track 6

DR LOVE: Would you comment on your editorial in the *JCO* about the response to gefitinib that was reported by Inoue and colleagues, which you termed the "Lazarus response" (Langer 2009)?

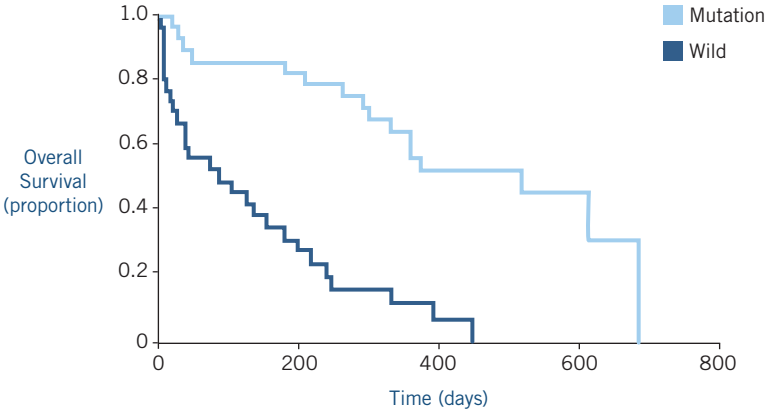
DR LANGER: They published an amazing paper in which they reported on first-line gefitinib in patients with advanced NSCLC harboring EGFR mutations who were ineligible for chemotherapy as a result of poor performance status. Their data showed that outcomes for the patients with mutation-positive disease who received gefitinib were nearly as good as what we see in patients with a performance status of 0 or 1.

The notion that a single oral agent, which 10 years ago was hardly on our radar screen, can induce response and "resurrect" these patients is novel. Although they were not cured, it provided these patients with a meaningful

quality of life and extended their survival from eight months to about one and a half years (Inoue 2009; [1.2]). It's clear that if a patient with mutation-positive, advanced NSCLC is not a candidate for chemotherapy, one should have no compunction whatsoever about administering an EGFR TKI.

1.2

Multicenter, Phase II Trial of First-Line Gefitinib for Patients with Advanced NSCLC Harboring EGFR Mutations with Poor Performance Status



"The median PFS, median survival time, and 1-year survival rate of the patients with sensitive EGFR mutations were 6.5 months, 17.8 months, and 63%, respectively. [This graphic] also shows a survival curve of 31 patients without EGFR mutations. Their median survival time was 3.5 months."

Originally published by the American Society of Clinical Oncology. Inoue A et al. *J Clin Oncol* 2009;27:1394-400.

Track 7

DR LOVE: How do you select therapy in the first-line metastatic setting based on EGFR mutation testing?

DR LANGER: Considering the IPASS data, I believe that patients who test positive for EGFR mutations should be offered the opportunity to receive an EGFR TKI up front. I wouldn't say that it's mandatory. If you examine the survival data in Dr Mok's paper, which are still somewhat immature, the profound response and progression-free survival (PFS) advantages have not yet translated into a survival benefit (Mok 2009). In some cases, the PFS exceeds one year or more. I can think of no cytotoxic combination that can generate a RECIST response rate of 65 to 80 percent.

Also, gefitinib spares patients the toxicity of chemotherapy. Patients still have to deal with diarrhea and rash, but I believe with time that we will learn how to manage these side effects more effectively.

DR LOVE: At ASCO a biomarker analysis from the IPASS study was presented that examined the significance of EGFR mutations, EGFR gene copy number by FISH and EGFR protein expression (1.3). Based on these data, it appears that if a patient's mutation status was negative but FISH-positive, gefitinib was not beneficial. What are your thoughts about that?

DR LANGER: Yes — clearly the key predictor was EGFR mutation status.

1.3

Phase III Trial Comparing First-Line Gefitinib to Carboplatin/Paclitaxel in Patients with Advanced NSCLC: Progression-Free Survival (PFS) by Biomarker Status

	PFS, HR[1]	*p*-value	PFS, Rx x subgroup interaction[2]
EGFR mutation status			
M+ (n = 261)	0.48	<0.0001	<0.0001
M- (n = 176)	2.85	<0.0001	
EGFR gene copy number			
FISH+ (n = 249)	0.66	0.0050	
FISH+, M+ (n = 190)	**0.48**	—	0.0437
FISH+, M- (n = 55)	**3.85**	—	
FISH- (n = 157)	1.24	0.2368	

[1] HR (hazard ratio) < 1.0 favors gefitinib; [2] HR in biomarker-positive versus HR in biomarker-negative

Fukuoka M et al. *Proc ASCO* 2009;**Abstract 8006**.

Track 8

DR LOVE: How do you approach selection of first-line systemic therapy for patients with advanced disease?

DR LANGER: For standard patients who present with de novo metastatic NSCLC with squamous histology, I prefer gemcitabine generally in combination with carboplatin.

For patients with predominantly adenocarcinomas, my preference is carboplatin in combination with paclitaxel or pemetrexed. If the patient is bevacizumab eligible, we've been grafting that onto the combination also.

I've been particularly impressed with the data reported by Patel and colleagues evaluating first-line carboplatin/pemetrexed and bevacizumab with maintenance pemetrexed and bevacizumab for NSCLC. Granted, they're Phase II data and come from a limited number of institutions, but these are still some of the more impressive data we've seen (Patel 2009; [1.4]).

An ongoing Phase III trial for patients eligible for bevacizumab is comparing carboplatin/pemetrexed/bevacizumab followed by maintenance bevacizumab and pemetrexed to carboplatin/paclitaxel/bevacizumab followed by maintenance bevacizumab in patients with Stage IIIB or IV NSCLC.

ECOG has a trial that we hope will open soon for patients who've already received the ECOG-E4599 regimen of carboplatin/paclitaxel/bevacizumab and are free of disease progression after four cycles. They will be randomly assigned to receive maintenance with bevacizumab versus pemetrexed versus the combination.

A purist could argue for a fourth arm, offering observation alone with crossover to the combination perhaps at the time of disease progression, but such a trial would not be able to accrue patients in the United States.

DR LOVE: In clinical practice in this situation, are you using bevacizumab alone for maintenance therapy, or are you combining it with pemetrexed?

DR LANGER: I have patterned my approach based on the Patel data, combining bevacizumab and pemetrexed. We have no Phase III data that prove this regimen is superior. Those data are pending, and the ongoing Phase III trial comparing maintenance bevacizumab to bevacizumab and pemetrexed will help determine whether adding pemetrexed is advantageous. ■

1.4

Pemetrexed/Carboplatin/Bevacizumab with Maintenance Pemetrexed and Bevacizumab for NSCLC

"The regimen achieved a median PFS of 7.8 months, and the entire PFS 95% CI exceeded the a priori assumption of a median PFS of 4.2 months. Additional outcomes included a response rate of 55% and median OS of 14.1 months. At a median follow-up of 13.0 months, 18 patients (36%) were still alive. Importantly, the regimen had a favorable toxicity profile. The majority of adverse events were observed during the initial six cycles of therapy, and the continuation of pemetrexed and bevacizumab beyond initial treatment was feasible."

PFS = progression-free survival; CI = confidence interval; OS = overall survival

Patel JD et al. *J Clin Oncol* 2009;27(20):3284-9.

SELECT PUBLICATIONS

Fukuoka M et al. **Biomarker analyses from a phase III, randomized, open-label, first-line study of gefitinib (G) versus carboplatin/paclitaxel (C/P) in clinically selected patients (pts) with advanced non-small cell lung cancer (NSCLC) in Asia (IPASS).** *Proc ASCO* 2009;**Abstract 8006**.

Inoue A et al. **First-line gefitinib for patients with advanced non-small-cell lung cancer harboring epidermal growth factor receptor mutations without indication for chemotherapy.** *J Clin Oncol* 2009;27:1394-400.

Langer CJ. **The "Lazarus response" in treatment-naïve, poor performance status patients with non-small-cell lung cancer and epidermal growth factor receptor mutation.** *J Clin Oncol* 2009;27(9):1350-4.

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

Patel JD et al. **Phase II study of pemetrexed and carboplatin plus bevacizumab with maintenance pemetrexed and bevacizumab as first-line therapy for nonsquamous non-small-cell lung cancer.** *J Clin Oncol* 2009;27(20):3284-9.

Socinski MA et al. **Safety of bevacizumab in patients with non-small-cell lung cancer and brain metastases.** *J Clin Oncol* 2009;27(31):5255-61.