INTERVIEW

Jyoti D Patel, MD

Dr Patel is Associate Professor of Medicine at Northwestern University in Chicago, Illinois.

Tracks 1-12

Track 1 Gender-related differences in the incidence, biology, prognosis and response/toxicity to treatment in NSCLC

Track 2 Phase II study results with pemetrexed/carboplatin and bevacizumab with maintenance pemetrexed/bevacizumab as first-line therapy for nonsquamous NSCLC

Track 3 PointBreak: A Phase III study of pemetrexed/carboplatin/bevacizumab followed by maintenance pemetrexed/bevacizumab versus the ECOG-E4599 regimen for Stage IIIB/IV nonsquamous NSCLC

Track 4 "Switch" and "continuation" maintenance therapy for NSCLC

Track 5 Approach to biomarker assessment and treatment for NSCLC

Track 6 Erlotinib-associated dermatologic toxicity, trichomegaly and metabolic changes

Track 7 ECOG-E6508: A Phase II study of BLP25 and bevacizumab in unresectable Stage IIIA/B nonsquamous NSCLC after definitive chemoradiation therapy

Track 8 **Case discussion:** A 63-year-old man and never smoker with adenocarcinoma of the lung and a solitary brain metastasis undergoes stereotactic radiosurgery followed by treatment with carboplatin/pemetrexed and bevacizumab on a clinical trial

Track 9 **Case discussion:** A 50-year-old woman and never smoker has an EGFR-mutant adenocarcinoma of the lung and cardiac tamponade with extreme shortness of breath

Track 10 **Case discussion:** A 48-year-old woman with a remote smoking history is diagnosed with EGFR wild-type metastatic NSCLC and receives carboplatin/paclitaxel and bevacizumab followed by bevacizumab on the PointBreak study

Track 11 Mutual exclusivity of K-ras, EGFR and ALK mutations in NSCLC

Track 12 Preferred adjuvant chemotherapy regimens in NSCLC

Select Excerpts from the Interview

Tracks 2-3

DR LOVE: Would you discuss your study that evaluated the combination of pemetrexed/carboplatin and bevacizumab as first-line therapy for NSCLC and the ongoing Phase III trial with this regimen?

DR PATEL: We developed a single-arm Phase II study of the combination of pemetrexed/carboplatin and bevacizumab (Patel 2009). The eligibility criteria were similar to the ECOG-E4599 study of carboplatin/paclitaxel and bevacizumab — no brain metastasis, no anticoagulation, PS 0 to 1 and no squamous histology. Patients received six cycles of chemotherapy followed by continued pemetrexed and bevacizumab maintenance therapy.

The idea was that pemetrexed was a little gentler. It doesn't yield the taxane toxicities, such as neuropathy and myelosuppression, so we could administer prolonged therapy and improve outcomes.

We were impressed with the toxicity profile, but more impressive were the tremendous radiographic responses we observed in more than half of the patients. The median survival was approximately 14 months (3.1). It is interesting to note that three patients developed diverticulitis, but it didn't seem to be a vasculitic phenomenon, so we amended the study such that patients with a history of diverticulitis could no longer enroll. After that, we saw no further issues.

We've now developed a Phase III trial that has completed accrual. The PointBreak study includes 900 patients randomly assigned to four cycles of carboplatin/paclitaxel/bevacizumab followed by bevacizumab maintenance therapy or carboplatin/pemetrexed/bevacizumab followed by pemetrexed/bevacizumab maintenance therapy (3.2).

DR LOVE: Do you have initial data from this trial in terms of quality-of-life side effects, particularly on the maintenance phase with pemetrexed/bevacizumab versus bevacizumab?

DR PATEL: We have not yet shared the data, but I can speak from anecdotal experience. Patients who have controlled disease tend to fare well with prolonged pemetrexed treatment. Five to seven percent experience a tremendous amount of fatigue, and we usually identify those patients early. I'm most excited about this approach because, in almost 20 percent of patients, after we stopped the carboplatin we continued to see a response with only pemetrexed and bevacizumab.

3.1

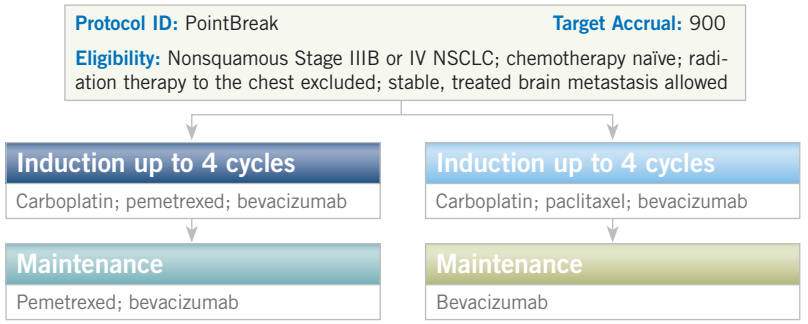
Efficacy Results from a Phase II Study of First-Line Carboplatin, Pemetrexed and Bevacizumab Followed by Maintenance Pemetrexed and Bevacizumab in Nonsquamous Non-Small Cell Lung Cancer

Treatment outcomes	N = 49	Percent
Objective response	27	55%
Complete response	1	2%
Partial response	26	53%
Progression-free survival	7.8 mo (5.2-11.5)	—
Overall survival	14.1 mo (10.8-19.6)	—

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

3.2

Phase III Study of Chemotherapy/Bevacizumab Followed by Maintenance Therapy for Advanced Non-Small Cell Lung Cancer (NSCLC)



Primary endpoint: Overall survival

www.clinicaltrials.gov. Identifier NCT00762034.

DR LOVE: Do you have any other thoughts on the issue of maintenance therapy in general?

DR PATEL: Another approach is called "switch maintenance," although it may more accurately be early second-line therapy. Induction therapy is administered, and then at the completion of four to six cycles it is followed with an agent that has been approved using the switch paradigm — either erlotinib or pemetrexed. Survival benefits were observed in studies using this tactic (Ciuleanu 2009; Cappuzzo 2010), and it is a reasonable approach. Many would argue that if a patient is followed closely and scans or chest x-rays are conducted fairly often, you would be able to find minimal disease progression before the patient became symptomatic and thus administer equal amounts of a second drug with a similar survival outcome. However, catastrophic events can occur and 30 percent of patients may never move on to that second-line agent using this strategy.

For patients who have demonstrated responses to initial therapy, often I find that continuation of the first drug makes sense. With pemetrexed many of us have been doing just that. We don't have enough data on true "continuation maintenance" to make a good argument for it, but intuitively it makes sense — and it works.

Track 7

DR LOVE: Would you describe the BLP25 liposomal vaccine and how it is being studied in NSCLC?

DR PATEL: BLP25 is a vaccine targeting the mucinous — or MUC — glycoproteins expressed in almost all NSCLC tumors. A randomized Phase II study evaluated patients with at least localized cancer and some radiation therapy

(Butts 2005, 2007). When they evaluated patients with locally advanced disease, they found a survival improvement. That led to a large Phase III trial, the START trial, which is currently ongoing in patients with locally advanced NSCLC who receive definitive chemoradiation therapy (3.3).

Administration of the vaccine is interesting because a small amount of cyclophosphamide is administered prior to the vaccine to increase its immunogenicity. The vaccine is administered in four injections every three weeks initially and then every six weeks.

We are conducting a Phase I/II study evaluating bevacizumab in combination with the vaccine among patients who've undergone definitive chemoradiation therapy with weekly paclitaxel and carboplatin followed by two cycles of consolidation carboplatin and paclitaxel. We then administer a combination of bevacizumab for two years with the vaccine. The rationale for this approach stems from evidence that bevacizumab increases T-cell function and antigen presentation. We believe it may make the vaccine more effective. ■

3.3

Multicenter, Phase III, Randomized, Double-Blind, Placebo-Controlled Study of the Cancer Vaccine Stimuvax® (L-BLP25 or BLP25 Liposome Vaccine) in Unresectable Stage III Non-Small Cell Lung Cancer (NSCLC)

Protocol ID: NCT00409188
Target Accrual: 1,476

Eligibility
Unresectable Stage III NSCLC with documented stable disease or objective response after chemoradiation therapy

R

Single infusion of cyclophosphamide → L-BLP25 qwk x 8 → maintenance L-BLP25

Single infusion of placebo → placebo qwk x 8 → maintenance placebo

Treatment continues until disease progression.
Primary endpoint: Survival

www.clinicaltrials.gov. Accessed February 24, 2011.

SELECT PUBLICATIONS

Butts C et al. **A multi-centre phase IIB randomized controlled study of BLP25 liposome vaccine (L-BLP25 or Stimuvax) for active specific immunotherapy of non-small cell lung cancer (NSCLC): Updated survival analysis B1–01.** *J Thorac Oncol* 2007;2(Suppl 4):332-3.

Butts C et al. **Randomized phase IIB trial of BLP25 liposome vaccine in stage IIIB and IV non-small-cell lung cancer.** *J Clin Oncol* 2005;23(27):6674-81.

Cappuzzo F et al. **Erlotinib as maintenance treatment in advanced non-small-cell lung cancer: A multicentre, randomised, placebo-controlled phase 3 study.** *Lancet Oncol* 2010;11(6):521-9.

Ciuleanu T et al. **Maintenance pemetrexed plus best supportive care versus placebo plus best supportive care for non-small-cell lung cancer: A randomised, double-blind, phase 3 study.** *Lancet* 2009;374(9699):1432-40.

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.