INTERVIEW

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CD 2, Tracks 7-24

Track 7 Cancer Genome Atlas Project's identification of mutations in squamous cell NSCLC

Track 8 Approach to first-line treatment and maintenance therapy for patients with advanced squamous cell NSCLC

Track 9 Guiding principles in the treatment of locally advanced NSCLC

Track 10 Chemotherapy options to combine with RT in the treatment of locally advanced NSCLC

Track 11 Results of CALGB-30407: A Phase II study of pemetrexed, carboplatin and RT with or without cetuximab for patients with locally advanced, unresectable NSCLC

Track 12 Proposed Alliance for Clinical Trials in Oncology study of targeted therapy with crizotinib or erlotinib followed by chemoradiation therapy in Stage III NSCLC

Track 13 PROCLAIM: A Phase III study of pemetrexed, cisplatin and RT followed by consolidation pemetrexed versus etoposide, cisplatin and RT followed by consolidation cytotoxic chemotherapy of physician's choice in Stage III nonsquamous NSCLC

Track 14 Duration of treatment in Stage III and Stage IV NSCLC

Track 15 Initial treatment with carboplatin/paclitaxel/bevacizumab followed by maintenance bevacizumab in advanced nonsquamous NSCLC without bevacizumab contraindications

Track 16 Clinical experience with first-line carboplatin/pemetrexed followed by pemetrexed maintenance in advanced nonsquamous NSCLC with contraindications to bevacizumab

Track 17 Consideration of targeted therapy with concurrent RT in lung cancer

Track 18 Targeting acquired resistance to EGFR TKIs in advanced NSCLC with the MET inhibitors onartuzumab and tivantinib

Track 19 Treatment decision-making after the identification of an EGFR mutation in patients who have initiated first-line chemotherapy

Track 20 Break Apart FISH Probe assay for ALK testing

Track 21 Rapidity of response to erlotinib versus chemotherapy in patients with highly symptomatic EGFR-mutant advanced NSCLC

Track 22 Management of EGFR-mutant advanced NSCLC in patients who demonstrate response to erlotinib but then experience slow disease progression

Track 23 Investigation of the molecular biology of relapsed SCLC

Track 24 Perspective on the benefits of lung cancer screening

Select Excerpts from the Interview

CD 2, Tracks 9-12

DR LOVE: What is your usual treatment approach for locally advanced NSCLC?

DR GOVINDAN: My principle is to make decisions about surgery early on because with a nonoperative therapy, full rather than interrupted doses of thoracic radiation therapy (TRT) can be administered. Next I would advocate for FDG-PET scanning because about 10% to 15% of patients with Stage III disease have occult Stage IV NSCLC, and we do not want these patients to be subjected to needless combined modality therapy.

Also, it is important to choose the right chemotherapy regimen. I would administer cisplatin rather than carboplatin in the definitive setting of chemoradiation therapy. The most time-tested regimen for which we have Phase III data is cisplatin/etoposide. I tend to use 2 cycles of cisplatin/etoposide with concurrent radiation therapy. In a Phase III study patients with Stage III NSCLC were randomly assigned to either 2 cycles of cisplatin/etoposide and TRT or the same regimen followed by 3 cycles of docetaxel. No improvement in survival was observed in patients who received docetaxel, but a 5% increase in death rate occurred (Hanna 2007).

DR LOVE: What other chemotherapy regimens are being used with radiation therapy?

DR GOVINDAN: For many years, weekly paclitaxel/carboplatin concurrent with radiation therapy and 2 cycles of induction and consolidation systemic therapy were administered. The use of systemic doses of paclitaxel/carboplatin with radiation therapy is another option. Paclitaxel/carboplatin every 3 weeks in combination with TRT is well tolerated. I've used that on occasions when cisplatin was not an option.

We have been studying pemetrexed in this setting because it has the advantage that it can be administered at full doses with radiation therapy. The Phase II CALGB-30407 trial evaluated pemetrexed/carboplatin every 3 weeks in combination with TRT. Four additional cycles of pemetrexed alone in the consolidation setting were administered after 4 cycles of doublet therapy in an attempt to optimize systemic therapy. Remarkably, approximately 50% of patients were able to receive all 8 cycles with a median survival of about 22 months (Govindan 2011).

DR LOVE: Do you approach chemoradiation therapy differently for squamous and nonsquamous NSCLC?

DR GOVINDAN: Regardless of histology, I currently use cisplatin/etoposide/radiation therapy off protocol. The Phase III PROCLAIM study will compare pemetrexed/cisplatin/radiation therapy followed by consolidation pemetrexed to etoposide/cisplatin/radiation therapy followed by consolidation cytotoxic chemotherapy of choice for locally advanced Stage III nonsquamous NSCLC.

CD 2, Tracks 15-16

DR LOVE: What is your initial treatment strategy for an otherwise healthy, young patient with nonsquamous, EGFR wild-type, ALK wild-type, advanced NSCLC?

DR GOVINDAN: If the patient meets the eligibility criteria for the ECOG-E4599 study, I would administer bevacizumab (Sandler 2006). For the vast majority of patients, pemetrexed seems to be appropriate. In terms of side effects, pemetrexed/carboplatin is better tolerated.

If I chose not to administer bevacizumab, I would opt for 2 cycles of pemetrexed/carboplatin, reevaluate the patient, add 2 more cycles if chemotherapy is well tolerated and then continue with pemetrexed maintenance therapy. In patients who have received prolonged pemetrexed, I observe 3 common side effects: fatigue, leg edema

and cytopenia. The leg edema is quite symptomatic, and I tend to manage it with diuretics, particularly furosemide. Occasionally, I've used short courses of steroids. I believe the pathophysiology involves vascular endothelial damage leading to leaky vessels, either in the lymphatics or in the venous circulation.

CD 2, Tracks 19, 21-22

DR LOVE: When you interact with medical oncologists in community practice, what are some of the most common questions they ask about NSCLC?

DR GOVINDAN: One common question I am asked is what to do for a symptomatic patient with metastatic NSCLC for whom chemotherapy has been initiated before EGFR mutation test results were available: If the EGFR mutation test results are found to be positive, what do I do?

My typical approach is to continue chemotherapy and administer erlotinib in the maintenance setting as long as patients are tolerating the chemotherapy well with no major side effects. No hard data indicate that this is the only acceptable approach. Some investigators feel compelled to change therapy right away to erlotinib. I suppose that's an option, but I have not done so.

On the other hand, if I have the EGFR mutation data before I start chemotherapy, I opt to go straight to erlotinib in the front-line setting. We now have a number of studies indicating that administering EGFR TKIs in the front-line setting improves response rates two- to threefold and increases progression-free survival compared to chemotherapy (Mok 2009; Rosell 2011; [3.1]).

DR LOVE: Would you administer chemotherapy or erlotinib to a patient with highly symptomatic EGFR-mutant advanced NSCLC in need of a rapid response?

DR GOVINDAN: When you administer an EGFR TKI to a patient with EGFR mutation-positive NSCLC, especially in the case of an exon 19 deletion, you see responses within days. I've had patients with impressive radiographic resolution within a week — multiple nodules in the lung disappearing within just a week.

Keep in mind, however, that even with the exon 19 deletion, the response rate with EGFR TKI inhibitors is not 100%. Even though the patient may have an EGFR mutation, other factors may be present that can influence response to EGFR TKI therapy. We don't have a good handle on the genomic landscape of EGFR-mutant NSCLC. Planning is under way for studies for patients with EGFR mutation-positive disease to evaluate all the other mutations that are coexistent in that patient population.

DR LOVE: What is your approach for a patient who has an EGFR mutation and has a great response to erlotinib but then slowly experiences disease progression?

DR GOVINDAN: I believe we should be performing rebiopsy for these patients because about half of them will have a T790M mutation (Oxnard 2011), for which we have some interesting trials in development. About 20% may have the MET amplification, and then other oncogenes may be active in this population. Outside a trial setting, I would consider continuing erlotinib in spite of disease progression and then adding chemotherapy. The idea is that different clones of cancer cells exist, and the EGFR mutant clone could resurface in the absence of erlotinib (Riely 2007; [3.2]). Unfortunately, these patients are likely to experience progression again fairly soon. ■

3.1

EURTAC: A Phase III Trial of First-Line Erlotinib versus Chemotherapy for Patients with Advanced Non-Small Cell Lung Cancer with EGFR Activating Mutations

	Erlotinib (n = 86)	Chemotherapy (n = 87)	Hazard ratio	*p*-value
Median progression-free survival	9.7 mo	5.2 mo	0.37	<0.0001
Median overall survival	22.9 mo	18.8 mo	0.80	0.42
Best overall response rate	58%	15%	—	—
Complete response rate	2%	0%	—	—
Partial response rate	56%	15%	—	—
Disease control rate	79%	66%	—	—

Rosell R et al. *Proc ASCO* 2011;**Abstract 7503**.

3.2

Changes in Tumor on CT and FDG-PET After EGFR Tyrosine Kinase Inhibitor (TKI) Discontinuation and Reinitiation in Patients with Non-Small Cell Lung Cancer Previously Responding to Erlotinib or Gefitinib

Median/mean change in:	After stopping EGFR TKI	After restarting EGFR TKI
Tumor diameter	+9%/+9%	-1%/1%
Tumor volume	+50%/+61%	-1%/-4%
Tumor SUV(max)	+18%/+23%	-4%/-11%

"In patients who develop acquired resistance, stopping erlotinib or gefitinib results in symptomatic progression, increase in SUV(max), and increase in tumor size.

Symptoms improve and SUV(max) decreases after restarting erlotinib or gefitinib, suggesting that some tumor cells remain sensitive to epidermal growth factor receptor blockade."

Riely GJ et al. *Clin Cancer Res* 2007;13(17):5150-5.

SELECT PUBLICATIONS

Govindan R et al. **Randomized phase II study of pemetrexed, carboplatin, and thoracic radiation with or without cetuximab in patients with locally advanced unresectable non-small-cell lung cancer: Cancer and Leukemia Group B trial 30407.** *J Clin Oncol* 2011;29(23):3120-5.

Hanna NH et al. **Phase III trial of cisplatin (P) plus etoposide (E) plus concurrent chest radiation (XRT) with or without consolidation docetaxel (D) in patients (pts) with inoperable stage III non-small cell lung cancer (NSCLC): HOG LUN 01-24/USO-023.** *Proc ASCO* 2007;**Abstract 7512**.

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

Oxnard GR et al. **Acquired resistance to EGFR tyrosine kinase inhibitors in EGFR-mutant lung cancer: Distinct natural history of patients with tumors harboring the T790M mutation.** *Clin Cancer Res* 2011;17(6):1616-22.

Rosell R et al. **Erlotinib versus chemotherapy (CT) in advanced non-small cell lung cancer (NSCLC) patients (p) with epidermal growth factor receptor (EGFR) mutations: Interim results of the European erlotinib versus chemotherapy (EURTAC) phase III randomized trial.** *Proc ASCO* 2011;**Abstract 7503**.

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.