INTERVIEW

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Tracks 1-12

Track 1 **Case discussion:** A physician and never smoker presents with a large pleural effusion and is diagnosed with EGFR-mutant adenocarcinoma of the lung and bone metastases

Track 2 Dosing of erlotinib for patients with EGFR mutations

Track 3 Afatinib in patients with the T790M mutation and acquired resistance to erlotinib

Track 4 Reinitiation versus continuation of erlotinib in patients who are sensitive or resistant to EGFR TKIs

Track 5 Adjuvant erlotinib in patients with Stage IIIA EGFR-mutant NSCLC

Track 6 Association between pack-years of cigarette smoking and EGFR mutation status

Track 7 Increasing number of targets for biomarker assessment in NSCLC

Track 8 Perspective on the benefits of nanoparticle albumin-bound (*nab*) paclitaxel in NSCLC

Track 9 Pros and cons of neoadjuvant chemotherapy for NSCLC

Track 10 Antitumor activity of bevacizumab alone in NSCLC

Track 11 Clinical approach to first-line and maintenance therapy for advanced NSCLC

Track 12 Therapeutic options for adjuvant chemotherapy in NSCLC

Select Excerpts from the Interview

Tracks 2, 4

DR LOVE: How do you approach dosing of erlotinib for patients with EGFR-mutant NSCLC?

DR RIZVI: Our goal by and large is for patients to receive full-dose erlotinib at 150 mg per day. We are able to manage cutaneous toxicities reasonably well in conjunction with our dermatology department. Even though erlotinib is an oral agent, the side effects are real and can be as significant as those with intravenous chemotherapy.

Many of our patients are not able to tolerate full-dose therapy, and we probably have about the same number of patients at 100 mg per day as their maximally tolerated dose as we do at 150 mg per day. We don't know whether

patients are more apt to develop resistance at 100 mg versus 150 mg, so we try to administer as full a dose as possible.

DR LOVE: What are your thoughts on the issue of re-treatment with erlotinib? What do we know about repeat responses in patients who've previously received an EGFR TKI?

DR RIZVI: Two scenarios relate to that. I have a patient with clinical Stage IIIA NSCLC and an EGFR mutation who chose erlotinib as adjuvant treatment.

No data support that, but with Stage IIIA disease and a high risk of recurrence, we chose to administer it. At two years we stopped the erlotinib, and approximately one year later he experienced a recurrence in the lung and lymph nodes.

At that point we resumed the erlotinib, and he was sensitive to it. He has been receiving it for about a year now and is maintaining a response to therapy. So he never was truly resistant to erlotinib — it was stopped at two years empirically and then, when he experienced a recurrence, we resumed it and he was sensitive again.

The second situation is someone who is receiving erlotinib for advanced-stage disease and experiences disease progression while receiving it. What do you do in that situation? Our experience has been that, to some extent, if you stop it, you may see a flare effect — the tumor may grow because a sensitive population of cells may remain (Riely 2007; [2.1]).

By and large, for patients who had initially sensitive but subsequently resistant disease we continue the erlotinib and add whatever our next course of chemotherapy might be to that regimen.

2.1

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.

Track 3

DR LOVE: Would you comment on what we know about the "irreversible" EGFR TKI BIBW 2992, or afatinib?

DR RIZVI: Afatinib is an irreversible TKI affecting EGFR and HER2, and earlier Phase I trials provided evidence that this agent may be more effective at targeting the T790M acquired-resistance mutation. The belief is that patients with a "sensitivity" EGFR mutation will invariably respond to erlotinib. However, with time eventually everyone will develop resistance through emergence of a secondary acquired-resistance mutation, which changes the conformation of the protein further and makes the cancer cell resistant to erlotinib.

Afatinib may be a more effective agent in terms of targeting that acquired-resistance mutation (Shih 2010). One trial is ongoing with afatinib as first-line therapy for patients with known sensitivity EGFR mutations. Another study is combining afatinib with cetuximab for patients who have developed acquired resistance to erlotinib.

Track 8

DR LOVE: What are your thoughts on the recent data with nanoparticle albumin-bound (*nab*) paclitaxel in NSCLC, particularly the favorable results seen in advanced squamous cell NSCLC?

DR RIZVI: Our own earlier Phase II experience was as a first-line, single-agent, weekly therapy in the older, not as good performance status (PS)-type of patient population with advanced NSCLC. We experienced a good outcome (Rizvi 2008).

The more recent data with *nab* paclitaxel — particularly in patients with squamous histology — show an extremely important result (Socinski 2010b). I don't know how to explain it, and we are not routinely using *nab* paclitaxel for our patients, but I believe it would be worth studying *nab* paclitaxel for the population of patients with squamous cell disease.

Our institutional guidelines limit the use of *nab* paclitaxel to patients with an intolerance or a reaction to standard taxane therapy. However, our threshold is low and we switch to *nab* paclitaxel if patients experience any sort of reaction with paclitaxel.

Track 11

DR LOVE: How do you generally approach first-line treatment for patients with advanced NSCLC?

DR RIZVI: Our group has been fairly uniform in terms of our approach to first-line therapy for Stage IV non-EGFR-mutated adenocarcinoma of the

lung. Most of our patients are receiving pemetrexed/cisplatin or pemetrexed/carboplatin with bevacizumab as first-line therapy.

For patients with squamous cell disease, most are receiving gemcitabine and a platinum agent or a taxane and a platinum agent as first-line treatment. We've always favored cisplatin as opposed to carboplatin as first-line therapy, although it's more difficult to administer taxanes in combination with cisplatin because patients encounter problems with diarrhea from docetaxel, renal compromise from cisplatin and neuropathy from both.

Pemetrexed has been fairly easy to combine with cisplatin, and we've found that patients fare extremely well while receiving this therapy. It's been a nice match in terms of tolerability.

Patients with adenocarcinoma receive pemetrexed/cisplatin and bevacizumab as first-line therapy. My practice has been to drop the cisplatin after four to six cycles and continue the pemetrexed and bevacizumab as maintenance therapy. Patients can continue with this combination for a long time.

I am currently treating a couple of 80-year-old patients who are receiving pemetrexed/bevacizumab maintenance therapy, and they've been responsive. As long as the PS is reasonable, even the elderly patients have been faring well.

Most patients prefer receiving maintenance therapy. I believe that more patients have conceptual difficulties with discontinuing chemotherapy after four or six cycles. The discontinuation is unsettling for patients, and our patients welcome being able to continue active maintenance treatment. ■

SELECT PUBLICATIONS

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.

Reynolds C et al. **Phase II trial of nanoparticle albumin-bound paclitaxel, carboplatin, and bevacizumab in first-line patients with advanced nonsquamous non-small cell lung cancer.** *J Thorac Oncol* 2009;4(12):1537-43.

Riely GJ et al. **Prospective assessment of discontinuation and reinitiation of erlotinib or gefitinib in patients with acquired resistance to erlotinib or gefitinib followed by the addition of everolimus.** *Clin Cancer Res* 2007;13(17):5150-5.

Rizvi NA et al. **Phase I/II trial of weekly intravenous 130-nm albumin-bound paclitaxel as initial chemotherapy in patients with stage IV non-small-cell lung cancer.** *J Clin Oncol* 2008;26(4):639-43.

Shih J et al. **Activity of BIBW2992, an irreversible EGFR/HER1 and HER2 TKI, in lung adenocarcinoma patients harboring less common EGFR mutations.** *Proc ESMO* 2010;**Abstract 415P**.

Socinski MA et al. **A dose finding study of weekly and every-3-week *nab*-paclitaxel followed by carboplatin as first-line therapy in patients with advanced non-small cell lung cancer.** *J Thorac Oncol* 2010a;5(6):852-61.

Socinski MA et al. **Results of a randomized, phase III trial of *nab*-paclitaxel (*nab*-P) and carboplatin (C) compared with Cremophor-based paclitaxel (P) and carboplatin as first-line therapy in advanced non-small cell lung cancer (NSCLC).** *Proc ASCO* 2010b;**Abstract LBA7511**.