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Lung Cancer™ UPDATE

Conversations with Oncology Investigators

Bridging the Gap between Research and Patient Care

FACULTY INTERVIEWS

David E Gerber, MD
Robert C Doebele, MD, PhD
David R Gandara, MD
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EDITOR

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2 Audio CDs
Monograph

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OVERVIEW OF ACTIVITY

Lung cancer is the leading cause of cancer mortality in the United States for both men and women, resulting in more deaths than breast, prostate, colon and pancreatic cancer combined. Historically, progress in the screening, prevention and treatment of this disease has been limited, and approximately 85% of patients who develop lung cancer will die of it. Traditional chemotherapy, surgery and radiation therapy have had a modest effect on long-term outcomes, but the discovery of various mutations and biomarkers has led to the proliferation of novel targeted agents for lung cancer that have in turn led to improvements in disease-free and overall survival in select patient populations. Published results from ongoing and completed studies lead to the continual emergence of novel therapeutic strategies and changes in the indications for existing treatments. In order to offer optimal patient care — including the option of clinical trial participation — the practicing clinician must be well informed of these advances. Featuring information on the latest research developments along with expert perspectives, this CME program is designed to assist medical and radiation oncologists with the formulation of up-to-date clinical management strategies for the care of patients with lung cancer.

LEARNING OBJECTIVES

- Identify distinct subtypes of adenocarcinoma of the lung — including those with EGFR mutations, EML4-ALK gene fusions, ROS1 gene rearrangement and other recently identified driver mutations — and the approved and investigational treatment options for patients with these mutations.
- Formulate a rational approach for molecular testing of tumors to identify potential protocol and off-protocol treatment options for patients.
- Describe mechanisms of tumor resistance to EGFR tyrosine kinase inhibitors, and identify investigational therapeutic opportunities to circumvent this process.
- Develop an evidence-based approach to the selection of induction and maintenance biologic therapy and/or chemotherapy for patients with advanced non-small cell lung cancer (NSCLC).
- Recall the scientific rationale for ongoing investigation of novel agents or immunotherapeutic approaches in lung cancer, and counsel appropriately selected patients about study participation.

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INTERVIEW

David E Gerber, MD

Dr Gerber is Associate Professor of Internal Medicine in the Division of Hematology-Oncology at the University of Texas Southwestern Medical Center's Harold C Simmons Cancer Center in Dallas, Texas.

Tracks 1-13

Select Excerpts from the Interview

Tracks 2-3

DR LOVE: Would you review existing clinical trial data on the use of EGFR inhibitors for patients with surgically excised EGFR-mutant non-small cell lung cancer (NSCLC)?

DR GERBER: We've known about the efficacy of erlotinib in EGFR-mutant lung cancer for a long time, yet we don't know its role in the postoperative or adjuvant setting. The NCIC CTG BR19 study of adjuvant gefitinib or placebo had a target accrual of 1,242 patients with resected Stage IB to Stage IIIA lung cancer (Goss 2013). This study was stopped early because a concomitant Phase III trial of gefitinib failed to show a survival benefit. So only 503 patients were enrolled. Fewer than 20 patients had EGFR-mutant NSCLC. Gefitinib showed no benefit and possibly had a harmful effect,

but the number of patients with EGFR-mutant NSCLC was small and the confidence intervals were wide.

Clearly BR19 doesn't answer the question. We're awaiting the results of the double-blind Phase III RADIANT trial, which recently completed enrollment of about 1,000 patients (NCT00373425). The study used a 2:1 randomization to erlotinib or placebo after complete tumor resection with or without adjuvant chemotherapy for patients with Stage IB to IIIA NSCLC who have EGFR-mutant tumors.

DR LOVE: What is the rationale for and the design of the ongoing ALCHEMIST trial?

DR GERBER: The ALCHEMIST trial is a huge effort sponsored by the National Cancer Institute (NCI). It is evaluating the role of targeted therapy in molecularly defined subsets of patients with NSCLC after surgery, after postoperative chemotherapy (if indicated) and after postoperative radiation therapy (if indicated).

It's attempting to enroll patients and collect data from about 8,000 resected nonsquamous NSCLC cases. The effort is not limited to the NCI or NCI-designated cancer centers. We're hoping to secure widespread community participation to answer questions that we've had now for the better part of a decade.

Tissue samples from patients who have undergone surgery will be sent for central testing. For patients harboring EGFR mutations or ALK rearrangements, specific adjuvant trials are available (1.1). The Alliance group has a study of adjuvant erlotinib in EGFR mutation-positive NSCLC with a target accrual of 430 patients, and the ECOG trial of adjuvant crizotinib in ALK-positive NSCLC has a target accrual of 378 patients. For these 2 studies, the primary endpoint is overall survival (OS).

1.1

Phase II-III ALCHEMIST: Adjuvant Lung Cancer Enrichment Marker Identification and Sequencing Trial for Patients with Nonsquamous Non-Small Cell Lung Cancer

Trial category (ID)	ALCHEMIST — Screen component (A151216)	ALCHEMIST — ALK (ECOG-E4512)	ALCHEMIST — EGFR (A081105)
Target	Registry/intervention with biopsy at recurrence	ALK-positive	EGFR mutant
Prevalence	All comers	Approximately 5%	Approximately 10%
Target accrual (n)	6,000 to 8,000	378 (5% ineligible)	430 (5% ineligible)
Primary endpoint	N/A	Overall survival	Overall survival
Statistical power	N/A	80%	85%
1-sided α	N/A	0.025	0.05
Hazard ratio	N/A	0.67	0.67

Doroshow JH. Genomic Clinical Trials: NCI Initiatives. National Cancer Advisory Board Meeting 2013. Available at: **deainfo.nci.nih.gov/advisory/ncab/164_1213/Doroshow.pdf**.

Track 7

DR LOVE: What is your experience with the next-generation ALK inhibitor ceritinib (LDK378) in advanced NSCLC?

DR GERBER: A substantial number of patients with disease progression on crizotinib respond to the second-generation ALK inhibitors. I have fairly extensive experience with ceritinib on clinical trials (Shaw 2014; [1.2]).

I saw a patient in her mid-70s with ALK-positive NSCLC who had disease control for only about 4 months on crizotinib. When we discontinued her crizotinib, she was immediately enrolled on a trial of ceritinib and has experienced ongoing disease control for about 10 months.

The starting oral dose is 750 mg daily. At this dose, many patients experience diarrhea, nausea and in the long term develop transaminitis but typically do not experience a dramatic change in bilirubin levels. In my experience, the transaminitis is reversible. I tend to dose reduce from 750 mg to 600 mg daily. All of my patients have been able to tolerate that lower dose and have ongoing disease control for months thereafter.

Editors note: On April 29, 2014, the US Food and Drug Administration granted accelerated approval to ceritinib for the treatment of ALK-positive, metastatic NSCLC in patients who experience disease progression on or who are intolerant to crizotinib.

1.2

Phase I Trial of Ceritinib (LDK378) in Patients with Advanced ALK-Rearranged Non-Small Cell Lung Cancer

≥400 mg/day of ceritinib	All patients (n = 114)	Crizotinib pretreated (n = 80)	Crizotinib naïve (n = 34)
ORR	66 (58%)	45 (56%)	21 (62%)
Complete response	1 (1%)	1 (1%)	0 (0%)
Partial response	65 (57%)	44 (55%)	21 (62%)
Median PFS	7.0 months	6.9 months	10.4 months
750 mg/day of ceritinib*	**All patients (n = 78)**	**Crizotinib pretreated (n = 50)**	**Crizotinib naïve (n = 28)**
ORR	46 (59%)	28 (56%)	18 (64%)
Complete response	0 (0%)	0 (0%)	0 (0%)
Partial response	46 (59%)	28 (56%)	18 (64%)
Stable disease	14 (18%)	8 (16%)	6 (21%)
Progressive disease	8 (10%)	8 (16%)	0 (0%)
Unknown response	10 (13%)	6 (12%)	4 (14%)
Select Grade 3/4 adverse events	**All patients (n = 130)**	**400 mg/d (n = 14)**	**750 mg/d* (n = 81)**
Elevated ALT	27 (21%)	1 (7%)	19 (23%)
Elevated AST	14 (11%)	1 (7%)	10 (12%)
Diarrhea	9 (7%)	1 (7%)	6 (7%)
Elevated lipase level	9 (7%)	0 (0%)	8 (10%)
Nausea	7 (5%)	0 (0%)	6 (7%)
Fatigue	6 (5%)	0 (0%)	5 (6%)
Hypophosphatemia	4 (3%)	1 (7%)	2 (2%)

ORR = overall response rate; PFS = progression-free survival

* Established maximum tolerated dose

Shaw AT et al. *N Engl J Med* 2014;370(13):1189–97.

Tracks 12-13

DR LOVE: Would you discuss some of the clinical trial data evaluating maintenance therapy in advanced NSCLC?

DR GERBER: One key study was the PARAMOUNT trial in which patients received 4 cycles of induction cisplatin/pemetrexed (Paz-Ares 2013). Patients without progressive disease (PD) or intolerable toxicity were randomly assigned to maintenance pemetrexed or placebo. The study was notable for a clinically meaningful improvement in PFS and OS with maintenance pemetrexed. Patients on both arms of the study fared well. Only patients without PD after induction were randomly assigned to pemetrexed or placebo.

This explains why the results are different from those of the PointBreak trial (Patel 2013). Even though 72% of the patients assigned to placebo went on to receive therapy after disease progression, only 4% received pemetrexed. We know that pemetrexed is an effective, well-tolerated and convenient agent. An important question is whether a role exists for pemetrexed for a patient who has received platinum/pemetrexed and experienced disease control for several months before developing PD.

DR LOVE: How do you generally treat pan-wild-type nonsquamous lung cancer in the front-line setting?

DR GERBER: For a bevacizumab-eligible patient, no data favor one treatment over another. For patients with pan-wild-type NSCLC, I usually administer 6 cycles of induction carboplatin/paclitaxel/bevacizumab followed by bevacizumab maintenance therapy, consistent with the ECOG-E4599 trial. Carboplatin/pemetrexed/bevacizumab followed by pemetrexed/bevacizumab is also effective and well tolerated.

From the PointBreak study, we learned that OS is not different between the 2 regimens (Patel 2013). The response rate and severity of toxicities also did not differ significantly. With carboplatin/paclitaxel as the backbone, more alopecia and neuropathy will occur. With a pemetrexed backbone, more myelosuppression will occur. The use of up-front carboplatin/paclitaxel/bevacizumab reserves pemetrexed for use after PD if the patient has received maintenance bevacizumab. For a bevacizumab-ineligible patient with nonsquamous NSCLC, I would use a platinum/pemetrexed combination as first-line therapy. ■

SELECT PUBLICATIONS

Goss GD et al. **Gefitinib versus placebo in completely resected non-small-cell lung cancer: Results of the NCIC CTG BR19 study.** *J Clin Oncol* 2013;31(27):3320-6.

Patel JD et al. **PointBreak: A randomized phase III study of pemetrexed plus carboplatin and bevacizumab followed by maintenance pemetrexed and bevacizumab versus paclitaxel plus carboplatin and bevacizumab followed by maintenance bevacizumab in patients with stage IIIB or IV nonsquamous non-small-cell lung cancer.** *J Clin Oncol* 2013;31(34):4349-57.

Paz-Ares LG et al. **PARAMOUNT: Final overall survival results of the phase III study of maintenance pemetrexed versus placebo immediately after induction treatment with pemetrexed plus cisplatin for advanced nonsquamous non-small-cell lung cancer.** *J Clin Oncol* 2013;31(23):2895-902.

Shaw AT et al. **Ceritinib in ALK-rearranged non-small-cell lung cancer.** *N Engl J Med* 2014;370(13):1189-97.

Shaw AT et al. **Clinical activity of the ALK inhibitor LDK378 in advanced, ALK-positive NSCLC.** *Proc ASCO* 2013;**Abstract 8010**.

INTERVIEW

Robert C Doebele, MD, PhD

Dr Doebele is Associate Professor of Medicine in the Division of Medical Oncology at the University of Colorado School of Medicine and University of Colorado Cancer Center in Aurora, Colorado.

Tracks 1-11

Select Excerpts from the Interview

Track 1

DR LOVE: Would you comment on the mechanisms of resistance to EGFR and ALK inhibitors?

DR DOEBELE: ALK-positive disease is an exciting area that follows on the heels of successes we've had with targeted therapies for EGFR mutation-positive lung cancer. I actually consider them analogous situations, even though the rates of incidence of each mutation are different.

The analogies continue even with drug resistance, which is an area that I'm highly involved with and interested in. We observe kinase domain mutations and evidence of bypass signaling as mechanisms of drug resistance. This is going to be a key area — these subsets of lung cancer may be our best hope for turning this type of disease into a chronic illness because we do see such great responses with agents that target these mutations. We simply need a better understanding of the biology of these cancers so that we can either prevent or at least significantly delay drug resistance.

The easiest mechanism of resistance to understand is a kinase domain mutation, which is a secondary mutation that's selected out during treatment with these targeted therapies. These inhibit or prevent adequate drug binding so that the abnormal protein, whether it's ALK or EGFR, is able to signal despite the presence of the drug.

The rate of ALK kinase domain mutations is probably only about 25%, a little lower than what we observe in EGFR-mutant disease, with which T790M mutations are probably in the range of 50% to 60%. The other difference between the 2 disease entities is that there's a greater diversity of resistance mutations too, and that makes our job a bit more difficult in terms of pinpointing a mechanism of resistance.

Another mechanism of resistance is bypass signaling, by which the cancer cell turns to another kinase to drive cellular proliferation and metastasis. That type of resistance mechanism might require dual therapy with different targeted agents, whereas kinase mutations might respond more favorably to a more potent inhibitor.

Track 4

DR LOVE: Is pemetrexed more effective than other agents for patients with ALK-positive NSCLC whose disease has progressed on crizotinib?

DR DOEBELE: Some data indicate that pemetrexed may be particularly useful in patients with ALK-positive lung cancer. Our group had demonstrated that patients with ALK-positive lung cancer have a longer PFS on pemetrexed-based therapy compared to patients with EGFR- or KRAS-mutant or pan-wild-type disease (Camidge 2011).

2.1

PROFILE 1007: Results of a Phase III Study of Crizotinib versus Standard Second-Line Chemotherapy for Patients with Advanced ALK-Positive Non-Small Cell Lung Cancer

Response	Crizotinib (n = 172)	Pemetrexed (n = 99)	Docetaxel (n = 72)
Overall response rate	66%	29%	7%
Median progression-free survival (PFS)	7.7 mo	4.2 mo	2.6 mo

	Crizotinib (n = 172)		Chemotherapy (n = 171)	
Adverse events	Any grade	Grade 3 or 4	Any grade	Grade 3 or 4
Vision disorder	60%	0%	9%	0%
Diarrhea	60%	0%	19%	1%
Nausea	55%	1%	37%	1%
Vomiting	47%	1%	18%	0%
Edema	31%	0%	16%	0%
Fatigue	27%	2%	33%	4%
Dysgeusia	26%	0%	9%	0%
Dyspnea	13%	4%	19%	3%

Median PFS: Crizotinib versus pemetrexed or docetaxel, $p < 0.001$

Differences in response rate between crizotinib and pemetrexed or docetaxel were significant ($p < 0.001$).

Shaw AT et al. *N Engl J Med* 2013;368(25):2385-94.

In the PROFILE 1007 trial patients were randomly assigned to crizotinib or standard second-line chemotherapy with docetaxel or pemetrexed. The study demonstrated superiority of crizotinib compared to single-agent chemotherapies in response rate and PFS. However, the objective response rate was about 30% for patients with ALK-positive disease receiving single-agent pemetrexed (Shaw 2013; [2.1]). This is higher than the overall response rate of 12.8% with pemetrexed as second-line therapy in unselected patients with lung adenocarcinoma (Scagliotti 2009). Pemetrexed is well tolerated and can be administered for many cycles.

DR LOVE: Should we consider clinical trials with second-generation ALK inhibitors rather than chemotherapy for patients with ALK-positive lung cancer?

DR DOEBELE: If a clinical trial with a second-generation ALK inhibitor is available, I believe it's reasonable. These agents appear promising, with response rates that are higher than those with chemotherapy. However, a clinical trial may not be available for some patients. I prepare these patients for the inevitability that we will have to consider standard platinum-based chemotherapy a year or two down the road.

Tracks 6, 11

DR LOVE: What is known about the incidence of brain metastases and the effects of targeted therapies on brain metastases in patients with EGFR-mutant or ALK-positive NSCLC?

DR DOEBELE: When you consider brain metastases, you must think about incidence at diagnosis versus lifetime incidence. We investigated patterns of metastatic spread in subsets of NSCLC characterized by driver oncogenes like ALK and EGFR. Approximately 30% of patients had brain metastases at the time of diagnosis, and no molecular cohort of patients exhibited a predisposition to develop brain metastases (Doebele 2012). Because patients with EGFR mutations or ALK gene rearrangements are living longer, their lifetime incidence of brain metastasis is higher.

One of the common sites of disease progression for patients who are receiving a targeted therapy is the central nervous system (CNS). CNS penetration of these agents is unpredictable, and the effective dose of drugs is lower than for other tissues in the body. All of the new next-generation inhibitors have shown some anecdotal data reporting responses in the CNS. The questions are how long the responses will last and whether those drugs have a problem with CNS penetration after long-term use.

For patients with small, asymptomatic brain metastases, it is reasonable to start therapy with crizotinib or an EGFR tyrosine kinase inhibitor (TKI). If the disease does not respond, some form of stereotactic radiosurgery might be a good approach to ablate metastatic disease while continuing the targeted therapy.

DR LOVE: What do we know about using high-dose pulses of EGFR TKIs for patients with advanced EGFR-mutant NSCLC and brain metastases?

DR DOEBELE: An article by Grommes and colleagues reported that a pulse dose of 1,500 mg of erlotinib administered once weekly resulted in a reasonable response in the CNS (Grommes 2011; [2.2]). I have administered pulse-dose erlotinib at 1,500 mg a week for a patient who had been receiving standard-dose erlotinib and had experienced problems with rash and diarrhea. This patient did not experience any rash during pulse-dose treatment, suggesting that pulsatile dosing may not cause the same toxicity.

2.2

Pulsatile High-Dose Weekly Erlotinib for Central Nervous System (CNS) Metastases from EGFR-Mutant Non-Small Cell Lung Cancer (NSCLC)

Response	N = 9
Best CNS response	
Partial response	67%
Stable disease	11%
Progressive disease	22%
Median time to CNS progression	2.7 mo
Median overall survival	12 mo

- Treatment was well tolerated.
- Major toxicities included rash, fatigue, diarrhea, nausea, hair thinning and asymptomatic intratumoral CNS hemorrhage.
- No Grade ≥3 toxicities were observed.

Conclusion: These results suggest that pulsatile erlotinib at approximately 1,500 mg per week is safe and has activity in patients with CNS disease from EGFR-mutant NSCLC even when systemic resistance has developed and been confirmed. Poor penetration of erlotinib when administered at standard low doses daily may explain in part the failure to achieve control of CNS metastases, rather than acquired resistance mutations such as T790M.

Grommes C et al. *Neuro-Oncology* 2011;13(12):1364-9.

Ongoing studies are exploring even higher doses — up to 2,000 mg of erlotinib. Another study of intermittent, high-dose afatinib to obtain better penetration of the drug for patients with EGFR-mutant NSCLC is also under way (NCT01647711).

Track 8

DR LOVE: Would you discuss your recent editorial "Time to shift the burden of proof for oncogene-positive cancer" (Doebele 2013)?

DR DOEBELE: The incidence of lung cancer driven by oncogenes is low. For example, the ROS1 fusion occurs in 1% to 2% of patients with NSCLC. The question going forward is whether our current model for drug development will benefit patients with oncogene-driven cancer.

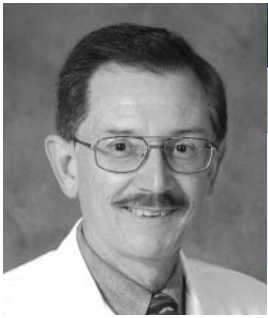
I believe we now have enough data to set a reasonably high bar for success so that we can obtain rapid approval of targeted therapies. We know that second-line chemotherapy for NSCLC typically produces response rates of 10% to 15% and a PFS of 3 to 4 months. Do we need randomized Phase III trials of targeted therapies versus chemotherapy if we see response rates of 50% to 60% and PFS of greater than 3 to 4 months with oncogene-targeted therapies? We need to think about new ways to bring targeted therapies to patients faster. As we recognize the heterogeneity of lung cancer and the success of targeted therapies, alternate approaches to approval should be considered. ■

SELECT PUBLICATIONS

Camidge DR et al. **Anaplastic lymphoma kinase gene rearrangements in non-small cell lung cancer are associated with prolonged progression-free survival on pemetrexed.** *J Thorac Oncol* 2011;6(4):774-80.

Doebele R. **Targeted therapies: Time to shift the burden of proof for oncogene-positive cancer?** *Nat Rev Clin Oncol* 2013;10(9):492-3.

Doebele R et al. **Oncogene status predicts patterns of metastatic spread in treatment-naïve non-small cell lung cancer.** *Cancer* 2012;118(18):4502-11.



INTERVIEW

David R Gandara, MD

Dr Gandara is Professor of Medicine, Director of the Thoracic Oncology Program and Senior Advisor to the Director at UC Davis Comprehensive Cancer Center in Sacramento, California.

Tracks 1-11

Select Excerpts from the Interview

Tracks 1-3

DR LOVE: What do we know about KRAS mutations in NSCLC versus colorectal cancer (CRC)?

DR GANDARA: KRAS mutation patterns and their prevalence are different in NSCLC and CRC. In lung cancer, more KRAS mutations are associated with cigarette smoking. How KRAS mutations behave, their prognostic effects and the other proteins that associate with KRAS are also distinct. So the tumor type and the milieu of the tumor are important.

DR LOVE: Is KRAS a driver mutation in NSCLC, and what are the approaches to inhibit that pathway?

DR GANDARA: A driver mutation is important in carcinogenesis and would have prognostic significance. If a targeted therapy against the mutation were available, it would have predictive value also. I believe that KRAS is a driver mutation in lung cancer, although that is currently under debate.

We do not have a specific inhibitor of KRAS. Most therapies focus on targeting proteins further downstream in the pathway. For example, MEK inhibitors are effective against KRAS-mutated lung cancers. A study by Jänne and colleagues demonstrated a significantly better objective response and PFS for patients with KRAS-mutant advanced NSCLC treated with the MEK1/MEK2 inhibitor selumetinib in combination with docetaxel versus docetaxel alone (Jänne 2013).

We recently reported that the combination of the MEK inhibitor trametinib with docetaxel elicited approximately a 30% response in patients with both KRAS-mutant and wild-type lung cancer. The type of KRAS mutation was important. All 10 patients with the G12C mutation, the most common tobacco-related KRAS mutation, experienced tumor shrinkage. The response rate was 40%, and the disease control rate was 80% in this group of patients (Gandara 2013).

Track 7

DR LOVE: What are your thoughts about rebiopsying a tumor in recurrent NSCLC?

DR GANDARA: For a patient with oncogene-driven cancer, rebiopsy of the tumor should be performed after the first EGFR TKI fails. Will earlier rebiopsy of a tumor help to determine if resistance is emerging and suggest therapy would need to be altered? Some interesting data were presented in support of this idea, and it follows up on our own work detecting these driver mutations in plasma DNA.

Tony Mok and colleagues performed a retrospective analysis of the concordance between EGFR mutations detected in tumor specimens and those detected from plasma DNA samples from the FASTACT-2 study (Mok 2013; [3.1]). Tests revealed approximately a 90% concordance. After 3 months of erlotinib-based therapy, the blood was reanalyzed. Those patients who had cleared the mutation experienced a long PFS. The patients with persistence of the mutation quickly experienced therapy failure. This is an

3.1

Concordance of EGFR Mutation Analysis between Tumor and Plasma Samples in the FASTACT-2 Study of Intercalated Chemotherapy with Erlotinib versus Chemotherapy with Placebo for Advanced Non-Small Cell Lung Cancer

EGFR activating mutations	p-EGFR mutation-positive (plasma)	p-EGFR mutation-negative (plasma)	Total
t-EGFR mutation-positive (tumor)	69	21	90
t-EGFR mutation-negative (tumor)	5	129	134
Total	**74**	**150**	**224**

p-EGFR mutation = EGFR mutation status by plasma DNA analysis; t-EGFR mutation = EGFR mutation status by tissue DNA analysis

Study conclusions

- Concordance rate between tests on tumor and plasma samples is high (88%).
- The predictive power of EGFR mutations in plasma DNA for treatment outcome is similar to that with tumor tissue.
- EGFR mutation analysis of plasma DNA is a potential alternative method for patients with inadequate tumor tissue.

Mok T et al. *Proc ASCO* 2013;**Abstract 8021**.

example of being able to detect a plasma marker that will help to determine if therapy needs to be changed.

Tracks 9-10

DR LOVE: Would you discuss the background and rationale for the lung cancer Master Protocol initiative?

DR GANDARA: About 2 years ago, the Lung Cancer Thoracic Malignancy Steering Committee — the NCI committee for directing trials — met to discuss the issue of developing better clinical trials. One of the conclusions of that meeting was that we needed master protocols. This is a protocol that would encompass a large group of patients with a certain category of cancer, include a genomic analysis and place those patients on multiple different experimental treatment regimens depending on what was found in each patient's cancer. If we're successful in lung cancer, we will take this concept into other tumor types and globalize it. We have to show that the strategy can work and that we can efficiently screen more than 1,000 patients per year. We're starting with squamous cell lung cancer because that's an area of unmet need.

The Lung Master Protocol, or SWOG-S1400, is set to launch soon and will focus on patients with advanced squamous cell cancer. Each of the arms of the Master Protocol is a Phase II/III trial that will genomically screen patients. If an arm clears an intermediate hurdle in a comparison to a standard therapy, it proceeds to Phase III. At the end of the day, if a trial is positive for PFS, that agent and that biomarker will be FDA approved. So if we're screening more than 1,000 patients a year and we have 6 arms open at the same time and the prevalence of a genomic biomarker varies from 2% to 40%, we project a hit rate of at least 65% to 70%. This means that a physician who puts a patient through this process will have at least a 65% to 70% chance of matching that patient with a treatment. You might ask, "What about that 30% who didn't match?" We've tried to anticipate that. We have a "nonmatch arm." Our first nonmatch arm will evaluate an anti-PD-L1 agent.

The goal is to develop an infrastructure that becomes self-sustaining. Let's assume that the study agent on arm 1 is not effective and doesn't meet its interim endpoint. That arm closes and a new arm 1 is applied, or we can add arms. We're hoping that 10 years from now if this initiative is successful, we will have changed the way we do business in drug development and we will be able to get better drugs to patients faster and more cost efficiently. ■

SELECT PUBLICATIONS

Gandara D et al. **Oral MEK1/MEK2 inhibitor trametinib (GSK1120212) in combination with docetaxel in KRAS-mutant and wild-type (WT) advanced non-small cell lung cancer (NSCLC): A phase I/Ib trial.** *Proc ASCO* 2013;**Abstract 8028**.

Jänne PA et al. **Selumetinib plus docetaxel for KRAS-mutant advanced non-small-cell lung cancer: A randomised, multicentre, placebo-controlled, phase 2 study.** *Lancet Oncol* 2013;14(1):38-47.

Maus MK et al. **KRAS mutations in non-small-cell lung cancer and colorectal cancer: Implications for EGFR-targeted therapies.** *Lung Cancer* 2014;83(2):163-7.

Mok T et al. **Detection of EGFR-activating mutations from plasma DNA as a potent predictor of survival outcomes in FASTACT 2: A randomized phase III study on intercalated combination of erlotinib (E) and chemotherapy (C).** *Proc ASCO* 2013;**Abstract 8021**.

O'Byrne KJ et al. **Molecular biomarkers in non-small-cell lung cancer: A retrospective analysis of data from the phase 3 FLEX study.** *Lancet Oncol* 2011;12(8):795-805.

INTERVIEW

Geoffrey R Oxnard, MD

Dr Oxnard is Assistant Professor of Medicine at Harvard Medical School and Medical Oncologist at the Dana-Farber Cancer Institute in Boston, Massachusetts.

Tracks 1-13

Select Excerpts from the Interview

Track 2

DR LOVE: Can you review current efforts to target RET- and BRAF-mutant tumors?

DR OXNARD: All of the RET TKIs are "dirty" because they target multiple kinases. Vandetanib, sunitinib and sorafenib are well studied in lung cancer and effective in subsets of patients. However, they are associated with toxicities.

The use of BRAF inhibitors is an option, but these agents cause serious cutaneous toxicities. We've seen responses that are not as durable compared to those with crizotinib or erlotinib. The question is, for a relatively heavy smoker with adenocarcinoma,

is it worthwhile to hunt for the V600E mutation that's present in about 1% of NSCLC cases? If the V600E mutation is present, I believe it is appropriate to integrate a BRAF inhibitor into second- or third-line care as available drugs start to wane in efficacy. The NCCN guidelines state that one can consider vemurafenib or dabrafenib in V600E-mutant NSCLC. The more targetable V600E BRAF mutation is more common in nonsmokers, whereas the less targetable non-V600E mutations are more enriched in smokers, especially in patients with squamous cell cancer.

Track 5

DR LOVE: Would you talk about the activity of afatinib in patients with uncommon EGFR mutation-positive or wild-type NSCLC?

DR OXNARD: We don't know if afatinib is more effective than erlotinib or gefitinib for these patients, but if I'm going to administer a first-line EGFR inhibitor for a patient who prefers such an approach to chemotherapy, perhaps I will reach for afatinib. It has more potency against wild type and potentially more potency against uncommon EGFR mutations.

Afatinib is active against wild-type EGFR and against HER2, based on preclinical models suggesting it has broader effects that likely lead to some of its toxicity. Erlotinib is dosed in such a way that it has some of that wild-type activity. Gefitinib is administered at a lower dose with less of that wild-type activity. We are trying to piece together the preclinical and clinical data to make these decisions, and based on the broader activity of afatinib against a couple of targets, I believe it's reasonable to use it in these rare populations for whom you want the agent with the most "punch."

However, the overall picture is somewhat murky, and if the patient's not a "gambler," I believe the standard of care for first-line therapy with these rare mutations is chemotherapy, saving the TKI as a maintenance or second-line therapy.

Track 9

DR LOVE: What are your thoughts on the combination of afatinib/cetuximab in EGFR-mutant NSCLC with acquired resistance to TKI therapy?

DR OXNARD: To date, the most potent EGFR-directed regimen is the combination of afatinib with cetuximab, which results in a good response rate of approximately 30% and an impressive waterfall plot (Janjigian 2012).

Compared to erlotinib, afatinib may cause increased toxicity for some patients. Cetuximab has its own toxicity profile, wherein more rash may mean more drug effect. When afatinib is added to cetuximab, more significant toxic effects are observed. Afatinib/cetuximab can be administered if a response is needed. The important question is whether such a combination will produce better results than the more familiar carboplatin/pemetrexed regimen, which elicits reliable effects.

If a patient receiving afatinib has become comfortable with the side effects, an intuitive next step would be to add cetuximab and see if that helps to regain a response. Switching a patient who's been receiving erlotinib to afatinib/cetuximab may pose a bigger challenge in terms of toxicity. Although it's a reasonable approach with a compelling rationale, it needs to be studied.

Track 11

DR LOVE: A recent press release suggested promising preliminary results from the Phase III REVEL trial of second-line ramucirumab in advanced NSCLC (4.1). What are your thoughts on the role of anti-VEGF therapy in NSCLC?

DR OXNARD: Ramucirumab is a novel VEGF inhibitor, and bevacizumab is approved for use in lung, colon and renal cell cancer. We have multiple VEGF antagonists in renal cell cancer and colon cancer. Studies have demonstrated that bevacizumab prolongs survival in cervical cancer, and ramucirumab prolongs survival in gastric cancer. The data with ramucirumab highlight the importance of continuing to target the VEGF pathway and to integrate anti-VEGF therapy with chemotherapy, although currently no biomarker exists to select patients for benefit.

The magnitude of benefit from anti-VEGF therapy is small compared to the huge responses observed with erlotinib or crizotinib in the right group of selected patients. I hope that we will be able to identify patients who will benefit from anti-VEGF agents in such a way that the benefits are dramatic rather than marginal like the responses currently being observed. Because of the increasing repertoire of anti-VEGF agents, making a choice is confusing, and it's unclear how to integrate one's choice into patient care.

4.1

REVEL: A Phase III Trial Evaluating Ramucirumab or Placebo in Combination with Docetaxel as Second-Line Therapy for Locally Advanced or Metastatic Non-Small Cell Lung Cancer

Protocol ID: NCT01168973

Accrual: 1,242 (Closed)

Eligibility

- Disease progression during or after 1 prior first-line platinum-based chemotherapy with or without maintenance therapy
- ECOG PS 0-1

R

- Docetaxel + ramucirumab
- Docetaxel + placebo

Primary endpoint: Overall survival (OS)

Key secondary endpoints: Progression-free survival (PFS), objective response rate

Press Release (2/19/14): REVEL showed statistically significant improvements in the primary endpoint of OS and secondary PFS endpoint in the ramucirumab/docetaxel arm compared to the control arm of placebo/docetaxel. Data will be presented at an upcoming scientific meeting and submitted to regulatory authorities in 2014.

www.clinicaltrials.gov, May 2014.

Track 12

DR LOVE: Currently, what first-line therapy do you generally recommend for your patients with metastatic squamous cell lung cancer?

DR OXNARD: The approved regimen for squamous cell lung cancer is cisplatin/gemcitabine. For a young and fit patient, that is what I'd administer. For a patient who is ineligible for cisplatin, a fairly common scenario in squamous cell lung cancer, I would likely administer carboplatin/paclitaxel. Notably, this combination is not FDA

approved, so it's an off-label use. *Nab* paclitaxel was recently approved based on a Phase III trial in which it demonstrated a better response rate than carboplatin/solvent-based paclitaxel (Socinski 2012).

Although carboplatin/solvent-based paclitaxel is conveniently administered every 3 weeks, carboplatin/*nab* paclitaxel is a weekly regimen. These regimens have different toxicity profiles (Socinski 2013; [4.2]). Solvent-based paclitaxel requires steroid therapy, whereas *nab* paclitaxel requires none.

This is a conversation that I have with my patients. *Nab* paclitaxel is becoming more widely used because it confers a greater chance of response, does not require steroids and is easier on the kidneys. Each regimen has different rules, and I make my decision based on what the patient needs. ■

4.2

Analysis of Efficacy and Safety of Weekly *Nab* Paclitaxel in Combination with Carboplatin (*nab*-P/C) as First-Line Therapy for Patients with Advanced Squamous Cell Non-Small Cell Lung Cancer

Outcome	*nab*-P/C (n = 229)	sb-P/C (n = 221)	Response rate ratio (RRR) or hazard ratio (HR)	*p*-value
ORR	94 (41%)	54 (24%)	RRR 1.680	<0.001
Median PFS	5.6 months	5.7 months	HR 0.865	0.245
Median OS	10.7 months	9.5 months	HR 0.890	0.284
Hematologic adverse events	***nab*-P/C** (n = 222)		**sb-P/C** (n = 214)	
	Grade 3	Grade 4	Grade 3	Grade 4
Anemia	20%	6%	4%	<1%*
Neutropenia	32%	11%	34%	17%
Thrombocytopenia	18%	4%	4%	3%*
Nonhematologic adverse events	***nab*-P/C** (n = 226)		**sb-P/C** (n = 218)	
	Grade 3	Grade 4	Grade 3	Grade 4
Fatigue	4%	0%	6%	0%
Sensory neuropathy	3%	0%†	11%	<1%
Alopecia	<1%	0%	0%	0%
Febrile neutropenia	<1%	0%	0%	<1%

sb-P/C = solvent-based paclitaxel with carboplatin; ORR = overall response rate; PFS = progression-free survival; OS = overall survival

* $p < 0.05$ in favor of sb-P/C, combined Grade 3/4 adverse events

† $p < 0.05$ in favor of *nab*-P/C, combined Grade 3/4 adverse events

Socinski MA et al. *Ann Oncol* 2013;24(9):2390–6.

SELECT PUBLICATIONS

Janjigian YY et al. **Activity of afatinib/cetuximab in patients (Pts) with EGFR mutant non-small cell lung cancer (NSCLC) and acquired resistance (AR) to EGFR inhibitors.** *Proc ESMO* 2012;**Abstract 1227O**.

Lazzari C et al. **PROSE: Randomized proteomic stratified phase III study of second-line erlotinib versus chemotherapy in patients with inoperable non-small cell lung cancer.** *Proc ASCO* 2013;**Abstract LBA8005**.

Socinski MA et al. **Weekly *nab*-paclitaxel in combination with carboplatin versus solvent-based paclitaxel plus carboplatin as first-line therapy in patients with advanced non-small-cell lung cancer: Final results of a phase III trial.** *J Clin Oncol* 2012;30(17):2055–62.

QUESTIONS (PLEASE CIRCLE ANSWER):

1. **The Phase III RADIANT trial is evaluating _____ versus placebo after complete tumor resection with or without adjuvant chemotherapy for patients with Stage IB to IIIA NSCLC who have EGFR-positive tumors.**
   a. Gefitinib
   b. Erlotinib
   c. Crizotinib

2. **ALCHEMIST is a national endeavor to conduct one integrated program for the molecular screening of patients with resected nonsquamous NSCLC and will identify patients with tumors harboring _____ for enrollment on specific adjuvant trials.**
   a. ALK rearrangements
   b. EGFR mutations
   c. Both a and b
   d. Neither a nor b

3. **Results of a Phase I trial of ceritinib for patients with advanced NSCLC harboring genetic alterations in ALK demonstrated an overall response rate of approximately 60% for patients with crizotinib-naïve and those with crizotinib-pretreated disease who received at least 400 mg of ceritinib daily.**
   a. True
   b. False

4. **Adverse events associated with the novel ALK inhibitor ceritinib when used at the maximum tolerated dose of 750 mg once daily include _____.**
   a. Diarrhea
   b. Nausea
   c. Fatigue
   d. Elevated transaminases
   e. All of the above

5. **The Phase III PROFILE 1007 study of crizotinib versus standard second-line chemotherapy for patients with advanced, ALK-positive NSCLC reported a statistically significant benefit for crizotinib versus chemotherapy with respect to _____.**
   a. Overall response rate
   b. PFS
   c. Both a and b

6. **Master Lung-1 (SWOG-S1400) is a Phase II/III biomarker-driven registration protocol for patients with _____ lung cancer moving to second-line therapy.**
   a. Nonsquamous cell
   b. Squamous cell
   c. Both a and b

7. **A study by Jänne and colleagues of selumetinib with docetaxel versus docetaxel alone demonstrated a significantly improved _____ for patients with KRAS-mutant advanced NSCLC.**
   a. Objective response
   b. PFS
   c. Both a and b

8. **Concordance rates between EGFR mutation tests on tumor and plasma samples from patients in the FASTACT-2 study of intercalated chemotherapy in combination with erlotinib versus chemotherapy with placebo for advanced NSCLC was found to be 88%.**
   a. True
   b. False

9. **The following mechanisms of resistance have been observed among patients with crizotinib-resistant ALK-positive disease:**
   a. Kinase domain mutations
   b. Bypass signaling
   c. Both a and b
   d. Neither a nor b

10. **A study by Socinski and colleagues evaluating *nab* paclitaxel/carboplatin versus solvent-based paclitaxel/carboplatin as first-line therapy for patients with advanced squamous cell lung cancer demonstrated a statistically significant improvement in _____ in favor of *nab* paclitaxel/carboplatin.**
    a. Overall response rate
    b. OS
    c. PFS
    d. All of the above

EDUCATIONAL ASSESSMENT AND CREDIT FORM

Lung Cancer Update — Issue 1, 2014

Research To Practice is committed to providing valuable continuing education for oncology clinicians, and your input is critical to helping us achieve this important goal. Please take the time to assess the activity you just completed, with the assurance that your answers and suggestions are strictly confidential.

PART 1 — Please tell us about your experience with this educational activity

How would you characterize your level of knowledge on the following topics?

4 = Excellent 3 = Good 2 = Adequate 1 = Suboptimal

	BEFORE	AFTER
Effectiveness of the investigational agent ceritinib (LDK378) in patients with crizotinib-naïve and crizotinib-resistant, ALK-positive, advanced NSCLC	4 3 2 1	4 3 2 1
Improvement in OS with the addition of the anti-VEGF monoclonal antibody ramucirumab to docetaxel for patients with locally advanced or metastatic NSCLC	4 3 2 1	4 3 2 1
Master Lung-1 (SWOG-S1400): A Phase II/III biomarker-driven registration protocol for patients with squamous cell NSCLC moving to second-line therapy	4 3 2 1	4 3 2 1
ALCHEMIST (Adjuvant Lung Cancer Enrichment Marker Identification and Sequencing Trial) to identify EGFR mutations and/or ALK rearrangements in patients with nonsquamous NSCLC	4 3 2 1	4 3 2 1
Improved response rate with first-line *nab* paclitaxel/carboplatin compared to standard solvent-based paclitaxel/carboplatin in advanced squamous cell carcinoma of the lung	4 3 2 1	4 3 2 1

Was the activity evidence based, fair, balanced and free from commercial bias?

☐ Yes ☐ No

If no, please explain: .....

Please identify how you will change your practice as a result of completing this activity (select all that apply).

☐ This activity validated my current practice
☐ Create/revise protocols, policies and/or procedures
☐ Change the management and/or treatment of my patients
☐ Other (please explain): .....

If you intend to implement any changes in your practice, please provide 1 or more examples:

.....

.....

The content of this activity matched my current (or potential) scope of practice.

☐ Yes ☐ No

If no, please explain: .....

Please respond to the following learning objectives (LOs) by circling the appropriate selection:

4 = Yes 3 = Will consider 2 = No 1 = Already doing N/M = LO not met N/A = Not applicable

As a result of this activity, I will be able to:

- Identify distinct subtypes of adenocarcinoma of the lung — including those with EGFR mutations, EML4-ALK gene fusions, ROS1 gene rearrangement and other recently identified driver mutations — and the approved and investigational treatment options for patients with these mutations. . . . . 4 3 2 1 N/M N/A
- Formulate a rational approach for molecular testing of tumors to identify potential protocol and off-protocol treatment options for patients. . . . . 4 3 2 1 N/M N/A
- Describe mechanisms of tumor resistance to EGFR tyrosine kinase inhibitors, and identify investigational therapeutic opportunities to circumvent this process. . . . . 4 3 2 1 N/M N/A
- Develop an evidence-based approach to the selection of induction and maintenance biologic therapy and/or chemotherapy for patients with advanced non-small cell lung cancer (NSCLC). . . . . 4 3 2 1 N/M N/A
- Recall the scientific rationale for ongoing investigation of novel agents or immunotherapeutic approaches in lung cancer, and counsel appropriately selected patients about study participation. . . . . 4 3 2 1 N/M N/A

Please describe any clinical situations that you find difficult to manage or resolve that you would like to see addressed in future educational activities:

.....

Would you recommend this activity to a colleague?

☐ Yes ☐ No

If no, please explain: .....

Additional comments about this activity:

.....

As part of our ongoing, continuous quality-improvement effort, we conduct postactivity follow-up surveys to assess the impact of our educational interventions on professional practice. Please indicate your willingness to participate in such a survey.

☐ Yes, I am willing to participate in a follow-up survey.
☐ No, I am not willing to participate in a follow-up survey.

PART 2 — Please tell us about the faculty and editor for this educational activity

4 = Excellent 3 = Good 2 = Adequate 1 = Suboptimal

Faculty	Knowledge of subject matter	Effectiveness as an educator
David E Gerber, MD	4 3 2 1	4 3 2 1
Robert C Doebele, MD, PhD	4 3 2 1	4 3 2 1
David R Gandara, MD	4 3 2 1	4 3 2 1
Geoffrey R Oxnard, MD	4 3 2 1	4 3 2 1
Editor	**Knowledge of subject matter**	**Effectiveness as an educator**
Neil Love, MD	4 3 2 1	4 3 2 1

Please recommend additional faculty for future activities:

.....

Other comments about the faculty and editor for this activity:

.....

.....

.....

REQUEST FOR CREDIT — Please print clearly

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