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Lung Cancer™ UPDATE

Conversations with Oncology Investigators
Bridging the Gap between Research and Patient Care

FACULTY INTERVIEWS

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EDITOR

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CONTENTS

2 Audio CDs
Monograph

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Lung Cancer Update
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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. 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. However, the advent of biologic and immunotherapeutic agents in lung cancer has led to recent 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 oncologists and radiation oncologists with the formulation of up-to-date clinical management strategies for the care of patients with lung cancer.

LEARNING OBJECTIVES

- Develop an evidence-based approach to the selection of induction and maintenance therapy for patients with advanced non-small cell lung cancer.
- Recall the scientific rationale for ongoing investigation of novel agents or immunotherapeutic approaches in lung cancer, and counsel appropriately selected patients about study participation.
- Employ an understanding of next-generation sequencing to determine its clinical and/or research application for patients with metastatic lung cancer.
- Describe mechanisms of tumor resistance to EGFR tyrosine kinase inhibitors, and identify therapeutic opportunities to circumvent this process.
- Identify patients with 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 incorporate approved and investigational treatment options into the care of these individuals.

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TABLE OF CONTENTS

FACULTY INTERVIEWS

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EDITOR

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INTERVIEW

Pasi A Jänne, MD, PhD

Dr Jänne is Director of the Lowe Center for Thoracic Oncology at the Dana-Farber Cancer Institute, Professor of Medicine at Harvard Medical School and Scientific Director at the Belfer Institute for Applied Cancer Science in Boston, Massachusetts.

Tracks 1-17

Select Excerpts from the Interview

Tracks 1-2

DR LOVE: What is the rationale behind using serologic assays to detect and monitor tumor mutations in patients with advanced non-small cell lung cancer (NSCLC)?

DR JÄNNE: As cancer cells grow and divide, they shed their DNA, and when you're dealing with cancer that has a mutation you can find that DNA in the patient's blood. The DNA is certainly coming from the cancer because these mutations are cancer

specific. This can potentially be used as a tool not only to diagnose noninvasively with a so-called liquid biopsy but also, ultimately, to perhaps monitor the disease.

This procedure is easier to perform than multiple serial biopsies. I believe we have technologies now that weren't available even a couple of years ago. When a patient's disease acquires resistance to targeted therapy, often biopsies may not be feasible or the results may take too long to obtain. Being able to obtain the same information from a blood sample and receive a rapid answer has real clinical importance and value.

DR LOVE: Recently it seems that the paradigm has shifted toward the use of biopsies, when possible, for patients receiving first-line EGFR tyrosine kinase inhibitor (TKI) therapy who then experience disease progression. At this point, do you consider that standard, even in the community setting?

DR JÄNNE: We now know that the third-generation EGFR inhibitors, such as osimertinib (AZD9291) or rociletinib (CO-1686), work much better in individuals who have the T790M EGFR mutation compared to those who do not. Mutation status is important to know because that would dictate which direction to go with treatment if you have access to these agents or, through a clinical trial, to many of the others that are currently under clinical development. Once these agents become commercially available, then biopsy does become a standard practice.

DR LOVE: Do you believe we may experience a transient phase in which biopsies will be indicated and that these kinds of serum assays will soon rapidly replace repeat biopsies?

DR JÄNNE: We are able to perform these serum tests more rapidly than next-generation sequencing (NGS), and this ability is a real game changer in the management of lung cancer and many other solid tumors. That said, many of the technologies can't capture the gene rearrangements. For that you need a sequencing-based technology. Some emerging technologies are able to do this. We haven't seen them yet in clinical applications, but the hope is that we will also have access to these.

Tracks 3-4

DR LOVE: What have your group and others reported on the efficacy and side effects of osimertinib?

DR JÄNNE: Osimertinib is clearly an effective agent with efficacy at multiple dose levels, from 20 to 240 mg daily. In our study for patients with NSCLC and acquired resistance to EGFR TKIs, patients with T790M-mutation positive disease had a higher objective response rate (ORR, 59% versus 29%) and progression-free survival (PFS, 13.1 months versus 5.6 months) than those without that mutation (Jänne 2015; [1.1]).

Although this class of agents is more selective for the mutant form than the wild-type form of EGFR, as we increased the dose we started to see some inhibitory effects on wild-type EGFR. However, at high doses osimertinib causes Grade 3 or higher rash and diarrhea, so 80 mg daily is the recommended Phase II dose.

The ORR is 21% with osimertinib in the population of patients without the T790M mutation. Some of that could be attributed to a re-treatment effect in patients who had previously received an EGFR TKI. If you specifically evaluate the individuals who immediately came off an EGFR TKI before trial entry, the ORR was only 11%. The median PFS for patients with T790M-negative NSCLC was 2.8 months.

DR LOVE: Would you discuss the data your group presented evaluating this agent as first-line therapy for advanced EGFR mutation-positive NSCLC and the other avenues being explored with this agent currently?

DR JÄNNE: The question is, for a patient with NSCLC previously untreated with an EGFR TKI, what is the response rate or PFS with osimertinib? The results of the AURA study of osimertinib as first-line therapy were presented at the 2015 ASCO meeting (Ramalingam 2015; [1.1]). Interestingly, the ORR was about 70%. Although the PFS rates were promising, it's too early to determine the median PFS.

The ongoing Phase III AURA 3 trial is evaluating osimertinib versus chemotherapy for patients with EGFR T790M mutation-positive advanced NSCLC after disease progression on an EGFR TKI (NCT02151981). Also, the randomized Phase III FLAURA trial evaluating osimertinib versus gefitinib or erlotinib as initial therapy for EGFR-mutant lung cancer is ongoing (NCT02296125).

1.1 **Phase I/II AURA Trial: Efficacy and Safety Results with Osimertinib (AZD9291) in Patients with EGFR Mutation-Positive Locally Advanced or Metastatic Non-Small Cell Lung Cancer**

	Dose-escalation and expansion cohorts[1]			First-line cohort[2]
Response	**All patients** (n = 239)	**T790M-positive** (n = 127)	**T790M-negative** (n = 61)	**All patients** (n = 60)
ORR (evaluable)	51%	61%	21%	73%
DCR (evaluable)	84%	95%	61%	97%
Survival	**n = 222**	**n = 138**	**n = 62**	**n = 60**
Median PFS	8.2 months	9.6 months	2.8 months	Not reached
Select AEs (Grade ≥3)	**20 mg daily** (n = 21)	**80 mg daily** (n = 90)	**160 mg daily** (n = 63)	**All patients** (n = 60)
Rash	0%	0%	3%	2%
Diarrhea	0%	1%	2%	3%
Nausea	5%	0%	0%	2%
Decreased appetite	5%	1%	0%	0%
Fatigue	5%	0%	0%	0%

ORR = objective response rate; DCR = disease control rate; PFS = progression-free survival; AEs = adverse events

[1] Jänne PA et al. *N Engl J Med* 2015;372(18):1689-99; [2] Ramalingam SS et al. *Proc ASCO* 2015;**Abstract 8000**.

Track 5

DR LOVE: What is known about the efficacy and safety of rociletinib in NSCLC?

DR JÄNNE: In the Phase I/II trial presented by Dr Sequist at ASCO 2015, the response rate with rociletinib in patients with T790M-positive disease was about 60% (Sequist 2015; [1.2]). This is similar to the response rate observed in the Phase I/II AURA trial. Finding the right dose for this agent has been challenging. Treatment-related toxicities include hyperglycemia and QTc prolongation, which have forced the use of lower doses. Reasonable activity was observed in patients with T790M-negative NSCLC. Whether this is due to the effect of the agent or to heterogeneity among the tumor cells is unknown.

1.2

Efficacy and Safety Results from a Phase I/II Trial of Rociletinib (CO-1686) for Patients with EGFR-Mutated Non-Small Cell Lung Cancer After Failure of an EGFR Inhibitor

Outcome (any dose)	**T790M-positive** (n = 46)	**T790M-negative** (n = 17)
ORR	59%	29%
DCR	93%	59%
Median PFS	13.1 months	5.6 months
Select adverse events (n = 92)*	**Any grade**	**Grade 3**
Hyperglycemia	47%	22%
Nausea	35%	2%
Fatigue	24%	4%
Diarrhea	22%	0%
Vomiting	14%	2%
QTc prolongation	12%	5%

* Therapeutic dose of rociletinib (500, 625, 750, 900 and 1,000 mg BID)

ORR = objective response rate; DCR = disease control rate; PFS = progression-free survival; QTc = QT interval corrected for heart rate

Sequist LV et al. *N Engl J Med* 2015;372(18):1700–9.

Track 11

DR LOVE: What is your perspective on the results of the Phase III PROCLAIM trial evaluating pemetrexed/cisplatin and thoracic radiation therapy (TRT) versus etoposide/cisplatin/TRT followed by consolidation chemotherapy for patients with previously untreated locally advanced NSCLC (Senan 2015; [1.3])?

DR JÄNNE: Oncologists have been administering etoposide/cisplatin with TRT for a long time. These data supported the use of pemetrexed/cisplatin/TRT but did not demonstrate superiority with etoposide/cisplatin/TRT. Some differences are apparent in the toxicity profile. No Grade 3 or higher alopecia occurred with pemetrexed/cisplatin. Another advantage with pemetrexed/cisplatin is that it can be administered once every 3 weeks, whereas etoposide is administered for 5 consecutive days every 4 weeks. After seeing these data, I will certainly start to use pemetrexed/cisplatin/TRT in my practice.

Tracks 15-17

DR LOVE: Would you discuss the differential effect of afatinib based on the presence of deletion 19 mutations versus the L858R EGFR mutation?

DR JÄNNE: In a pooled analysis, it seemed as if the patients who had an exon 19 deletion mutation had a greater survival advantage with afatinib compared to chemotherapy than did those with the L858R mutation (Yang 2015). Whether this is a class effect of EGFR TKIs is unknown. Two ongoing trials are addressing this question: LUX-Lung 7 (NCT01466660) and ARCHER-1050 (NCT01774721).

1.3

Phase III PROCLAIM Trial: Efficacy and Safety of Pemetrexed (Pem)/ Cisplatin (Cis)/Thoracic Radiation Therapy (TRT) versus Etoposide (Eto)/Cis/ TRT Followed by Consolidation Chemotherapy in Patients with Previously Untreated Locally Advanced Nonsquamous Non-Small Cell Lung Cancer

Outcome	Pem/cis/TRT (n = 301)	Eto/cis/TRT (n = 297)	Hazard ratio	*p*-value
Median OS	26.8 mo	25.0 mo	0.98	0.831
Median PFS	11.4 mo	9.8 mo	0.86	0.130
ORR	35.9%	33.0%	NR	0.458
DCR	80.7%	70.7%	NR	0.004
	Pem/cis/TRT (n = 283)		Eto/cis/TRT (n = 272)	
Select adverse events	All grades	Grade 3 or 4	All grades	Grade 3 or 4
Esophagitis	48.1%	15.5%	50.7%	20.6%
Abnormal neutrophil/granulocyte counts	42.8%	24.4%	54.8%	44.5%
Alopecia	8.1%	0%	36.0%	0.4%
Febrile neutropenia	5.7%	5.3%	10.3%	9.6%

OS = overall survival; PFS = progression-free survival; ORR = objective response rate; NR = not reported; DCR = disease control rate

Senan S et al. *Proc ASCO* 2015;**Abstract 7506**.

DR LOVE: Outside of a protocol setting, how do you select between afatinib and erlotinib?

DR JÄNNE: I typically use erlotinib. I believe afatinib is more toxic than erlotinib when used as initial therapy. It is not yet clear if afatinib will be better than erlotinib for patients with exon 19 deletion mutations. Until the results from the LUX-Lung 7 study are presented, I will continue to favor erlotinib.

DR LOVE: Do you believe afatinib/cetuximab has a role in EGFR T790M mutation-negative disease?

DR JÄNNE: Yes. In the initial study the ORR was approximately 25% for patients with T790M-negative disease and a bit more for those with T790M-positive NSCLC, with an overall PFS of about 4.7 months (Janjigian 2014). So this combination could potentially be used in T790M-negative disease. The challenge with this regimen is toxicity. The randomized Phase II/III SWOG-S1403 trial of first-line cetuximab/afatinib versus afatinib in advanced EGFR-mutant NSCLC (NCT02438722) is still ongoing. Whether that trial will be completed given the emergence of the third-generation EGFR TKIs remains to be determined. ■

SELECT PUBLICATIONS

Janjigian YY et al. **Dual inhibition of EGFR with afatinib and cetuximab in kinase inhibitor-resistant EGFR-mutant lung cancer with and without T790M mutations.** *Cancer Discov* 2014;4(9):1036–45.

Yang JC et al. **Afatinib versus cisplatin-based chemotherapy for EGFR mutation-positive lung adenocarcinoma (LUX-Lung 3 and LUX-Lung 6): Analysis of overall survival data from two randomised, phase 3 trials.** *Lancet Oncol* 2015;16(2):141–51.

INTERVIEW

Nasser H Hanna, MD

Dr Hanna is Associate Professor of Medicine at Indiana University in Indianapolis, Indiana.

Tracks 1-11

Track 1 **Case discussion:** A 55-year-old woman who initially received treatment for pan-wild-type adenocarcinoma of the lung found upon rebiopsy to harbor an ALK rearrangement receives crizotinib

Track 2 Appropriate use of next-generation sequencing

Track 3 Clinical experience with the next-generation ALK inhibitor ceritinib in crizotinib-naïve and crizotinib-resistant advanced NSCLC

Track 4 Approach to choice of maintenance regimen for patients with pan-wild-type adenocarcinoma of the lung

Track 5 Overall survival advantage with the recently FDA-approved anti-PD-1 agent nivolumab as compared to docetaxel for patients with advanced squamous NSCLC with disease progression on or after platinum-based chemotherapy

Track 6 **Case discussion:** A 44-year-old woman and heavy smoker with Stage IV squamous cell carcinoma (SCC) of the lung with disease progression on carboplatin/gemcitabine experiences a dramatic response to nivolumab

Track 7 Activity of nivolumab in adenocarcinoma of the lung

Track 8 Investigation of anti-PD-1 agents as first-line therapy in lung cancer

Track 9 Potential biomarkers for anti-PD-1 benefit

Track 10 Ongoing and planned clinical trials combining anti-PD-1/anti-PD-L1-based therapy with chemotherapy and/or radiation therapy

Track 11 Pros and cons of second-line therapy options (nivolumab versus ramucirumab/docetaxel versus docetaxel alone) for SCC of the lung

Select Excerpts from the Interview

Tracks 1-2

DR LOVE: Would you describe the current methodology for ALK testing and whether patients can be classified as ALK wild type initially but then be found to harbor an ALK rearrangement on rebiopsy?

DR HANNA: We have 3 methods to test for ALK. You can use immunohistochemistry, but that method is not validated nor FDA approved at this point. The gold standard is FISH. A FISH score of 0 obviously indicates ALK negativity. A score of 2+ or 3+ is almost always indicative of ALK positivity. A 1+ is more than likely negative, but a few ALK-positive cases have this score. You can perform PCR, but you may miss the fusion partner, and ALK has multiple partners. EML4 is the most common partner, but others exist.

DR LOVE: How do the available NGS platforms come into play here?

DR HANNA: Several NGS platforms are available. The most commonly used is FoundationOne®. We also use the PCDx™ test. All of these testing platforms claim some advantages compared to others. The company that makes FoundationOne has suggested that more ALK abnormalities are found than with other platforms, but we do not have any head-to-head comparisons. It's interesting that one platform may be better at detecting more of these ALK changes or EGFR mutations than others. This may contribute to a possible bias of some of the results.

DR LOVE: Is it reasonable to perform NGS testing on a biopsy sample from a nonsmoker that tested negative for EGFR mutations and ALK rearrangements by FISH analysis?

DR HANNA: Yes. That approach may lead to the discovery of mutations other than ALK. I have had a number of patients for whom such an approach paid off.

Track 3

DR LOVE: What are your thoughts on the next-generation ALK inhibitors, such as ceritinib? Where are these agents headed in the management of lung cancer?

DR HANNA: Ceritinib is now FDA approved for the treatment of ALK-positive metastatic NSCLC after disease progression on or intolerance to crizotinib. I believe it will also be approved in the up-front setting as it has been tested in pretreated and crizotinib-naïve disease (Kim 2014; [2.1]). It's highly active in both settings, with response rates of more than 50% and 60%, respectively. So, logically, one could conceive that ceritinib would be a more effective ALK inhibitor than crizotinib because it is so active after disease progression on crizotinib. However, a head-to-head comparison is needed to confirm this suggestion.

Ceritinib is a much more potent ALK inhibitor than crizotinib. Although crizotinib is an extremely potent MET inhibitor, it is not nearly as good as an ALK inhibitor. Crizotinib is probably a better ROS1-targeting agent than ceritinib. These drugs have distinct nuances. It's not a one-size-fits-all situation.

It is similar to the story of EGFR inhibitors. Patients with lung cancer receive erlotinib or afatinib if they have activating EGFR mutations. Even though we tend to lump all EGFR activating mutations together, a picture appears to be emerging suggesting that exon 19 and L858R are different, and so is their responsiveness to these agents (Yang 2015).

Ceritinib can be a tough drug, however. Nausea and diarrhea are the dominant, day-to-day side effects. If you hold the drug for 2 to 3 days, the nausea goes away. I've had patients who've experienced a great deal of difficulty tolerating ceritinib, but we've been able to dose reduce and use antiemetics. Because ceritinib is highly active, patients tend to put up with the side effects when they can and continue therapy.

Tracks 5-6

DR LOVE: Perhaps the biggest change in the field of oncology in a long time is the approval of an anti-PD-1 agent in lung cancer. What are your thoughts on the role of immune checkpoint inhibitors in NSCLC?

DR HANNA: We've had advances in lung cancer research with regard to things like the role of chemotherapy in the adjuvant and metastatic settings and the addition of chemo-

2.1

Phase I ASCEND-1 Trial: Efficacy and Safety of Ceritinib in Locally Advanced or Metastatic ALK-Positive Non-Small Cell Lung Cancer (NSCLC)

Clinical outcome	All patients (n = 246)	ALKi treated (n = 163)	ALKi naïve (n = 83)
Overall response rate	58.5%	54.6%	66.3%
Complete response	1.2%	1.2%	1.2%
Partial response	57.3%	53.4%	65.1%
Stable disease	6.5%	19.6%	22.9%
Median PFS	8.21 months	6.9 months	NE
12-month PFS	39.1%	28.4%	61.3%

Select AEs (n = 255)*	All grades	Grade 3 or 4
Diarrhea	86%	6%
Decreased hemoglobin	84%	5%
Nausea	80%	4%
Increased ALT	80%	27%
Increased AST	75%	13%
Fatigue	52%	5%
Increased blood glucose	49%	13%

* All patients received the maximum tolerated dose (750 mg/d), including 9 patients with cancers other than NSCLC.

ALKi = ALK inhibitor; PFS = progression-free survival; NE = not estimable; AEs = adverse events

Kim DW et al. *Proc ASCO* 2014;**Abstract 8003**.

therapy to radiation therapy for patients with Stage III disease, but I believe we'd all agree that these were modest advances.

Lung cancer oncologists tend to be more on the understated side. They don't tend to proclaim these huge advances. We can all agree that agents like crizotinib and erlotinib are major advances.

But the data with the anti-PD-1 antibody nivolumab as second-line therapy for squamous NSCLC are practice changing. In my 15 years of taking care of patients with lung cancer, this is the biggest "difference maker" that I've seen yet. The early results of the randomized Phase III CheckMate 017 trial of second-line nivolumab or docetaxel in squamous NSCLC compelled the Data Safety Monitoring Committee to recommend early closure because nivolumab made such a substantial difference (Brahmer 2015; [2.2]).

The hazard ratio for overall survival was 0.59 in favor of nivolumab. We simply don't see that in lung cancer and certainly not in patients with squamous cell carcinoma. Oddly enough, the tumors that have the highest mutational load, that are the most molecularly dirty, perhaps are those in which agents like PD-1/PD-L1 inhibitors will be most active.

We've now administered nivolumab to 30 patients at our center, and so far I have been impressed with the results. Our patients tend to be older in age, with a smoking history and comorbidities. So I was fearful of toxicities such as pneumonitis, colitis, hepatitis, rash, fevers and arthralgias. Surprisingly, I have not observed any Grade 2 or Grade 3 side effects. This is not to say that nivolumab is a totally benign agent. It certainly has side effects, but the patients I have cared for so far have tolerated it remarkably well.

2.2

CheckMate 017: Efficacy and Safety Results from a Phase III Trial of Nivolumab versus Docetaxel for Patients with Advanced Squamous Non-Small Cell Lung Cancer After Disease Progression on 1 Platinum-Based Chemotherapy

Outcome	Nivolumab (n = 135)	Docetaxel (n = 137)	Hazard ratio (HR)	*p*-value
Median OS	9.2 months	6.0 months	0.59	<0.001
Median PFS	3.5 months	2.8 months	0.62	<0.001
ORR	20%	9%	NR	0.008
CR	1%	0%	—	—
PR	19%	9%	—	—
Stable disease	29%	34%	—	—
Select adverse events	**Nivolumab** (n = 131)		**Docetaxel** (n = 129)	
	All grades	**Grade 3 or 4**	**All grades**	**Grade 3 or 4**
Fatigue	16%	1%	33%	8%
Asthenia	10%	0%	14%	4%
Nausea	9%	0%	23%	2%
Diarrhea	8%	0%	20%	2%
Pneumonitis	5%	0%	0%	0%
Arthralgia	5%	0%	7%	0%
Rash	4%	0%	6%	2%
Anemia	2%	0%	22%	3%
PN	1%	0%	12%	2%
Neutropenia	1%	0%	33%	30%
Febrile neutropenia	0%	0%	11%	10%

OS = overall survival; PFS = progression-free survival; ORR = objective response rate; NR = not reported; CR = complete response; PR = partial response; PN = peripheral neuropathy

Brahmer J et al. *N Engl J Med* 2015;373(2):123-35.

However, patients with autoimmune diseases or those with a history of pneumonitis should not receive these agents.

DR LOVE: Would you consider administering immune checkpoint inhibitors in the first-line setting?

DR HANNA: Randomized trials are ongoing with single-agent pembrolizumab (NCT02142738) or nivolumab (NCT02041533) versus chemotherapy in the up-front setting. With second-line nivolumab being much better than docetaxel, it's logical to think that it will be better than chemotherapy up front. The unanswered question is how to use it. Is it going to be better to combine it with chemotherapy? Should it be administered as a single agent before switching to or combining it with chemotherapy at disease progression? Should it be used as maintenance therapy? Although I am optimistic, we still need the data. ■

SELECT PUBLICATION

Yang JC et al. **Afatinib versus cisplatin-based chemotherapy for EGFR mutation-positive lung adenocarcinoma (LUX-Lung 3 and LUX-Lung 6): Analysis of overall survival data from two randomised, phase 3 trials.** *Lancet Oncol* 2015;16(2):141-51.

INTERVIEW

Joan H Schiller, MD

Dr Schiller is Professor and Chief in the Division of Hematology and Oncology, Deputy Director of the Simmons Comprehensive Cancer Center and Andrea L Simmons Distinguished Chair in Cancer Research at the University of Texas Southwestern Medical Center in Dallas, Texas.

Tracks 1-8

Select Excerpts from the Interview

Tracks 1-2

CASE DISCUSSION: A 59-year-old Hispanic woman and smoker with Stage IIIA adenocarcinoma of the lung who undergoes treatment with chemoradiation therapy

DR SCHILLER: This patient had been in a relatively good state of health until presenting with a 3-month history of cough and a 2-week history of hemoptysis. Workup revealed a 4-cm mass in the right main stem bronchus, about 2 centimeters from the carina. She also had multiple enlarged right-sided mediastinal lymph nodes and was diagnosed with a T3N2 Stage IIIA adenocarcinoma of the lung.

She received weekly carboplatin/paclitaxel with concurrent TRT followed by 2 cycles of consolidation carboplatin/paclitaxel. She experienced some dysphasia while receiving TRT, but that cleared relatively quickly. She did not experience any weight loss but did note some fatigue. Overall, she tolerated treatment well.

DR LOVE: What type of molecular testing for mutational changes was performed?

DR SCHILLER: We did not test for some of the driver mutations, because such testing has not yet been proven to be applicable to patients with Stage III disease who would

be receiving chemoradiation therapy. Molecular testing is an active area of investigation in this setting.

Debate is ongoing in the field about when to test for mutations and whether this should be done routinely. We have 2 reasons for not performing routine testing in this setting. First, this patient may never need to be tested if she is cured by the treatment she receives. Second, in this situation in which we do not have a lot of tumor, who knows what other mutations we may need to test for a couple years down the line? The tumor tissue will be archived for such purposes. The point of recurrent disease would be a good time to test for mutational changes.

DR LOVE: We've heard debate about the use of consolidation therapy after radiation therapy. Why did you administer carboplatin/paclitaxel consolidation therapy in this patient's case?

DR SCHILLER: My treatment choice was based on the results of the randomized Phase II LAMP trial for patients with unresected Stage IIIA/B NSCLC. The trial had 3 arms. Patients received 2 cycles of induction paclitaxel/carboplatin followed by TRT or 2 cycles of induction paclitaxel/carboplatin followed by weekly paclitaxel with concurrent TRT or weekly paclitaxel/carboplatin/TRT followed by 2 cycles of paclitaxel/carboplatin. In this trial, concurrent weekly paclitaxel/carboplatin and TRT followed by consolidation was associated with the best outcome (Belani 2005).

We must differentiate between weekly carboplatin/paclitaxel and any other weekly chemotherapy regimen when administering it for radiation-sensitizing purposes. You are not administering it to clear micrometastatic disease. That's why I believe you need standard doses at some point of the chemotherapy.

DR LOVE: What are the other alternatives to induction paclitaxel/carboplatin when using TRT?

DR SCHILLER: Another option is cisplatin/etoposide, which is the typical SWOG regimen, administered concurrently without any consolidation therapy (Gandara 2003). Standard doses are administered concurrently with TRT, with the idea of using this regimen, both as a radiation sensitizer and systemic therapy. However, it can be a tougher regimen to administer. Although one cannot compare across studies, the data are generally similar with these 2 regimens.

Track 6

CASE DISCUSSION: A 69-year-old man and smoker with extensive-stage small cell lung cancer (SCLC)

DR SCHILLER: This patient presented with cough, hemoptysis, fatigue and a 5-lb weight loss, all of which had occurred relatively quickly over several weeks. He had a large, bulky, 8-cm left-side mass invading into the left main stem bronchus. He also had liver metastases but no bone or brain metastases. He was diagnosed with extensive-stage SCLC. After receiving 4 cycles of cisplatin/etoposide, he had a marked tumor reduction in his liver and lung.

We also elected to administer prophylactic cranial irradiation, based on studies that show that even patients with extensive-stage disease, if they achieve a very good partial response, might also experience a survival benefit.

DR LOVE: Have there been any interesting data presented over the past several years on the treatment of SCLC, particularly with regard to the use of immune checkpoint inhibitors?

DR SCHILLER: SCLC has been an orphan disease for a while. The equivalent of the Lung-MAP trial (NCT02154490) for patients with SCLC is planned. This will be a trial in which the patient's tumor is collected and sequenced. Based on the sequencing data, the patient will be assigned to the appropriate agent.

Immune checkpoint inhibitors represent another interesting area. Data presented at the 2015 ASCO meeting demonstrated a promising response rate with immune-directed therapies in patients with SCLC (3.1). I believe that we're going to see a lot more interest in this area. The data suggest that with the immune checkpoint inhibitors, responses are observed in tumor types such as lung cancer — particularly in smokers — with high mutational load. ■

3.1

Efficacy and Safety of Immune Checkpoint Inhibitors in Recurrent[1] or Extensive-Stage[2] Small Cell Lung Cancer

	CheckMate 032[1]		KEYNOTE-028[2]
Outcome	**Nivo** (n = 40)	**Nivo + ipi** (n = 46)	**Pembro** (n = 20)
ORR	18%	17%	35%
Complete response	0%	2.2%	0%
Partial response	18%	15%	35%
Stable disease	20%	37%	5%
Overall survival	4.4 mo	8.2 mo	NR
Grade ≥3 AEs	**Nivo** (n = 40)	**Nivo + ipi** (n = 47)	**Pembro** (n = 20)
Fatigue	2.5%	0%	NR
Diarrhea	0%	8.5%	NR
Rash	0%	4.3%	NR
Pneumonitis	0%	2.1%	0%
Asthenia	NR	NR	5%
Increased bilirubin	NR	NR	5%
Colitis (Grade 5)	NR	NR	5%

Nivo = nivolumab; ipi = ipilimumab; pembro = pembrolizumab; ORR = objective response rate; NR = not reported; AEs = adverse events

Conclusions:

- Clinical responses with nivo with or without ipi regardless of PD-L1 expression[1]
- Promising antitumor activity with pembro in pretreated PD-L1-positive small cell lung cancer[2]

[1] Antonia SJ et al. *Proc ASCO* 2015;**Abstract 7503**; [2] Ott PA et al. *Proc ASCO* 2015;**Abstract 7502**.

SELECT PUBLICATIONS

Belani CP et al. **Combined chemoradiotherapy regimens of paclitaxel and carboplatin for locally advanced non-small-cell lung cancer: A randomized phase II locally advanced multi-modality protocol.** *J Clin Oncol* 2005;23(25):5883-91.

Gandara DR et al. **Consolidation docetaxel after concurrent chemoradiotherapy in stage IIIB non-small-cell lung cancer: Phase II Southwest Oncology Group study S9504.** *J Clin Oncol* 2003;21(10):2004-10.

INTERVIEW

Alex A Adjei, MD, PhD

Dr Adjei is Professor and Chair in the Department of Medicine, Senior Vice-President for Clinical Research and Katherine Anne Gioia Chair in Cancer Medicine at the Roswell Park Cancer Institute in Buffalo, New York.

Tracks 1-10

Select Excerpts from the Interview

Tracks 1-2

CASE DISCUSSION: A 60-year-old man and former smoker with Stage IIB adenocarcinoma of the lung treated with cisplatin/pemetrexed

DR ADJEI: The appropriate adjuvant therapy in this setting is somewhat controversial, but the evidence-based treatment is vinorelbine/cisplatin. This regimen has the most robust data in terms of benefit (Sève 2007). However, sometimes one needs to extrapolate a bit. An active chemotherapy regimen in the metastatic setting in most situations will be active in the adjuvant setting. In my practice, we tend to administer cisplatin/pemetrexed to patients with adenocarcinoma of the lung. This is based on our experience indicating that it is probably the best regimen for patients with metastatic adenocarcinoma of the lung.

DR LOVE: What is the probability that a patient with early-stage adenocarcinoma of the lung would complete the standard cycles of cisplatin/pemetrexed versus cisplatin/vinorelbine?

DR ADJEI: Patients may not be particularly fit after surgery, so it is appropriate to use an adjuvant chemotherapy regimen that is well tolerated and can be administered on

schedule to increase the feasibility that all necessary cycles will be received. The Phase II TREAT trial investigated adjuvant cisplatin in combination with pemetrexed or vinorelbine in early-stage NSCLC (Kreuter 2013; [4.1]). Cisplatin/vinorelbine can be immunosuppressive, so in some cases patients may be unable to receive treatment on schedule. Cisplatin/pemetrexed is better tolerated.

Most oncologists believe that chemotherapy doublets administered in the metastatic setting will elicit equivalent results as adjuvant therapy. The Phase III ECOG-E1505 (NCT00324805) trial is ongoing but closed to accrual. This study is evaluating adjuvant chemotherapy with or without bevacizumab for patients with completely resected Stage IB (≥4 cm) to Stage IIIA NSCLC.

It incorporates several chemotherapy regimens, including doublets that are thought to produce similar results in the metastatic setting, such as cisplatin/pemetrexed and cisplatin/gemcitabine. Results from this trial will shed more light on the effectiveness and safety of the different adjuvant chemotherapy regimens.

4.1

TREAT: Results of a Phase II Trial of Adjuvant Chemotherapy with Cisplatin/Pemetrexed (CPx) versus Cisplatin/Vinorelbine (CVb) in Early-Stage Non-Small Cell Lung Cancer

Key endpoints	**CPx** (n = 67)	**CVb** (n = 65)
Feasibility rate*	95.5%	75.4%
Deaths	1 (1.5%)	2 (3.1%)
Withdrawal of consent	0	4 (6.2%)
Dose-limiting toxicities	2 (3%)	10 (15.4%)
Select adverse events (Grade 3-4)	**CPx** (n = 67)	**CVb** (n = 65)
Anemia	0%	1.5%
Thrombocytopenia	0%	0%
Neutropenia	9%	69%
Nausea/vomiting	7.5%	5%
Fatigue	6%	5.5%
Renal impairment	3%	0%
Febrile neutropenia	1.5%	7.7%
Constipation	1.5%	0%
Thromboembolic events	1.5%	0%

*$p = 0.001$

Kreuter M et al. *Ann Oncol* 2013;24(4):986-92.

Tracks 4, 6-7

CASE DISCUSSION: A 50-year-old woman and never smoker with EGFR wild-type adenocarcinoma of the lung receives carboplatin/pemetrexed → pemetrexed maintenance

DR ADJEI: This patient presented in 2009 with a pleural effusion, a lung mass and a solitary vertebral metastasis. At that time the only molecular testing being performed

was for EGFR mutation, and her disease harbored the wild-type form of EGFR. Based on today's technology, we can't classify her disease as pan-wild-type. She received 4 cycles of carboplatin/pemetrexed and achieved a near-complete response. She then received maintenance pemetrexed. She also received zoledronic acid for the solitary bone metastasis, but this had to be discontinued because of some dental issues.

Her disease was responsive to treatment until early this year, when she started experiencing back pain. Upon MRI scanning, we discovered more bony disease. She received radiation therapy, went back on pemetrexed and is now faring well. It has been 6 years, and she's still receiving maintenance pemetrexed.

DR LOVE: Have you considered performing multiplex molecular testing for ALK or ROS1 rearrangement for this patient?

DR ADJEI: No, we do not have any archived tissue to test. Because of the significant shortness of breath at presentation, we had to rapidly perform a chest tube drainage of the pleural fluids by pleurodesis. The DNA sample used for EFGR molecular testing was from the collected effusion cell pellets. Also, because she's fared so well on treatment, we haven't performed other molecular tests.

DR LOVE: Why did you not switch treatment after discovering more bony metastases?

DR ADJEI: The MRI scans revealed the involvement of about 3 vertebrae. A suggestion of epidural disease was observed, but that wasn't clear. Because she had no other evidence of disease, we radiated the spine and continued with pemetrexed instead of switching to another type of treatment. Our plan is to keep her on pemetrexed until disease progression, after which we'll perform a biopsy and multiplex testing.

DR LOVE: What is your rationale for initially administering carboplatin/pemetrexed without bevacizumab? How do you currently approach bevacizumab therapy?

DR ADJEI: My experience through the years has been that the addition of bevacizumab to carboplatin/pemetrexed produces more toxic effects. Patients experience more fatigue, and after receiving 4 cycles of induction therapy the question arises whether to administer pemetrexed, bevacizumab or both as maintenance therapy. In some instances I have used both, but I find that when I do this, it is impossible for the patient to continue maintenance pemetrexed/bevacizumab for a long time. Because of the significant fatigue, maintenance therapy must be discontinued.

The Phase III PRONOUNCE trial reported no significant survival benefit between induction carboplatin/pemetrexed and paclitaxel/carboplatin/bevacizumab in patients with advanced nonsquamous NSCLC (Zinner 2015). This demonstrates that carboplatin/pemetrexed produces good results in patients with adenocarcinoma of the lung and the addition of bevacizumab does not add significant benefit. As such, in my practice I use carboplatin/pemetrexed. Generally, I use bevacizumab if I decide to treat with paclitaxel/carboplatin. ■

SELECT PUBLICATIONS

Sève P et al. **Class III beta-tubulin expression and benefit from adjuvant cisplatin/vinorelbine chemotherapy in operable non-small cell lung cancer: Analysis of NCIC JBR.10.** *Clin Cancer Res* 2007;13(3):994-9.

Zinner RG et al. **PRONOUNCE: Randomized, open-label, phase III study of first-line pemetrexed + carboplatin followed by maintenance pemetrexed versus paclitaxel + carboplatin + bevacizumab followed by maintenance bevacizumab in patients with advanced nonsquamous non-small-cell lung cancer.** *J Thorac Oncol* 2015;10(1):134-42.

QUESTIONS (PLEASE CIRCLE ANSWER):

1. **In the Phase I/II AURA trial of osimertinib (AZD9291) and the Phase I/II trial of rociletinib (CO-1686) for patients with EGFR mutation-positive advanced NSCLC, both investigational third-generation EGFR inhibitors demonstrated higher efficacy among patients with _____.**
   a. EGFR T790M mutation-positive disease
   b. EGFR T790M mutation-negative disease

2. **Results of the Phase III PROCLAIM trial for patients with previously untreated locally advanced nonsquamous NSCLC demonstrated a statistically significant improvement in _____ with pemetrexed/cisplatin/TRT versus etoposide/cisplatin/TRT followed by consolidation chemotherapy.**
   a. Median overall survival
   b. Median PFS
   c. Overall response rate
   d. All of the above
   e. None of the above

3. **The ongoing Phase II/III SWOG-S1403 trial is investigating afatinib with or without _____ for patients with newly diagnosed EGFR mutation-positive NSCLC.**
   a. Erlotinib
   b. Cetuximab
   c. Gefitinib
   d. Osimertinib
   e. Rociletinib

4. **The results of the Phase I ASCEND-1 trial of ceritinib in locally advanced or metastatic ALK-positive NSCLC demonstrated an overall response rate of more than 50% in the population of patients with _____.**
   a. ALK inhibitor-naïve disease
   b. ALK inhibitor-pretreated disease
   c. Both a and b
   d. Neither a nor b

5. **The Phase III PRONOUNCE trial for patients with advanced nonsquamous NSCLC demonstrated a statistically significant improvement in overall survival in favor of induction paclitaxel/carboplatin/bevacizumab versus carboplatin/pemetrexed.**
   a. True
   b. False

6. **In the Phase I/II CheckMate 032 trial of nivolumab with or without ipilimumab for patients with recurrent SCLC, the combination of nivolumab with ipilimumab demonstrated a promising ORR only in patients with tumors expressing high PD-L1 levels.**
   a. True
   b. False

7. **In the Phase Ib KEYNOTE-028 trial, pembrolizumab therapy was associated with Grade 3 or higher _____ in patients with extensive-stage SCLC.**
   a. Asthenia
   b. Increased bilirubin levels
   c. Colitis
   d. All of the above
   e. None of the above

8. **The results of the Phase II TREAT trial of adjuvant chemotherapy with cisplatin/pemetrexed versus cisplatin/vinorelbine for patients with early-stage NSCLC demonstrated _____.**
   a. A statistically significant improvement in the feasibility rate in favor of cisplatin/pemetrexed
   b. That cisplatin/vinorelbine is more immunosuppressive than cisplatin/pemetrexed
   c. Both a and b
   d. Neither a nor b

9. **The ongoing Phase III ECOG-E1505 trial is evaluating adjuvant chemotherapy with or without _____ for patients with completely resected Stage IB to Stage IIIA NSCLC.**
   a. Bevacizumab
   b. Nivolumab
   c. Crizotinib

10. **The Phase III CheckMate 017 trial of nivolumab versus docetaxel for patients with advanced squamous NSCLC after disease recurrence or progression on 1 platinum-based chemotherapy regimen demonstrated a statistically significant improvement in _____ with nivolumab.**
    a. Median overall survival
    b. Median PFS
    c. ORR
    d. All of the above

EDUCATIONAL ASSESSMENT AND CREDIT FORM

Lung Cancer Update — Issue 1, 2015

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
Overall survival advantage with the recently FDA-approved anti-PD-1 agent nivolumab as compared to docetaxel for patients with advanced squamous NSCLC with disease progression on or after platinum-based chemotherapy	4 3 2 1	4 3 2 1
Results of the Phase III PROCLAIM trial of cisplatin with either pemetrexed or etoposide and TRT → consolidation chemotherapy for locally advanced nonsquamous NSCLC	4 3 2 1	4 3 2 1
Activity and safety of new strategies (third-generation TKIs) and regimens (afatinib/cetuximab) for patients with acquired resistance to EGFR TKIs	4 3 2 1	4 3 2 1
Efficacy and tolerability of ceritinib, alectinib and other emerging ALK inhibitors in crizotinib-naïve and crizotinib-pretreated, ALK-rearranged NSCLC	4 3 2 1	4 3 2 1
Indications for the use of clinical assays and NGS in the identification of targetable mutations in NSCLC	4 3 2 1	4 3 2 1
Recent FDA approval of ramucirumab and integration into clinical algorithms for patients with squamous and nonsquamous NSCLC	4 3 2 1	4 3 2 1

Practice Setting:

☐ Academic center/medical school ☐ Community cancer center/hospital ☐ Group practice

☐ Solo practice ☐ Government (eg, VA) ☐ Other (please specify).....

Approximately how many new patients with lung cancer do you see per year? ..... patients

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:

- Develop an evidence-based approach to the selection of induction and maintenance therapy for patients with advanced non-small cell lung cancer. ..... 4 3 2 1 N/M N/A
- Recall the scientific rationale for ongoing investigation of novel agents or immuno-therapeutic approaches in lung cancer, and counsel appropriately selected patients about study participation. ..... 4 3 2 1 N/M N/A
- Employ an understanding of next-generation sequencing to determine its clinical and/or research application for patients with metastatic lung cancer. ..... 4 3 2 1 N/M N/A
- Describe mechanisms of tumor resistance to EGFR tyrosine kinase inhibitors, and identify therapeutic opportunities to circumvent this process. ..... 4 3 2 1 N/M N/A
- Identify patients with 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 incorporate approved and investigational treatment options into the care of these individuals. ..... 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:

.....

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.....

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Pasi A Jänne, MD, PhD	4 3 2 1	4 3 2 1
Nasser H Hanna, MD	4 3 2 1	4 3 2 1
Joan H Schiller, MD	4 3 2 1	4 3 2 1
Alex A Adjei, MD, PhD	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:

.....

.....

.....

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