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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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Sarah B Goldberg, MD, MPH
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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. 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 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 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 biologic therapy and/or chemotherapy for patients with advanced non-small cell lung cancer.
- Integrate newly approved agents for treatment in second- or later-line settings.
- Formulate an approach to incorporate newly approved checkpoint inhibitors into the treatment algorithm for patients with metastatic NSCLC.
- Employ an understanding of next-generation sequencing, and determine its clinical and/or research applicability for patients with metastatic lung cancer.
- Describe mechanisms of tumor resistance to EGFR tyrosine kinase inhibitors, and identify therapeutic options in this setting.
- Identify distinct subtypes of adenocarcinoma of the lung — including those with EGFR mutations, EML4-ALK gene fusions, ROS1 gene rearrangements and other recently identified driver mutations — and the approved and investigational treatment options for patients with these genetic abnormalities.

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EDITOR

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INTERVIEW

Lecia V Sequist, MD, MPH

Dr Sequist is Associate Professor of Medicine at Harvard Medical School in Boston, Massachusetts.

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CASE DISCUSSION: A 44-year-old woman and never smoker with previously treated Stage IV T790M-mutant adenocarcinoma of the lung experiences a very good partial response to a third-generation EGFR tyrosine kinase inhibitor (TKI) on a clinical trial

DR SEQUIST: The patient was a healthy, athletic mother of 4 who worked in a school and was having trouble breathing. She was seen at another center and found to have Stage IV EGFR exon 19 mutation-positive adenocarcinoma with bilateral pulmonary nodules and an adrenal metastasis. She achieved a quick response to first-line erlotinib, which was maintained for about 10 months. When her breathing started to worsen, she received afatinib for 2 months without any response.

The choice to administer afatinib after erlotinib is not evidence based. People believe that the newer drug should be used after the older one, but the data suggest that

afatinib can be a good first-line EGFR inhibitor. Once a patient has received either erlotinib or afatinib in the first line, I don't believe we gain much by switching to the other. The Phase IIb/III LUX-Lung 1 trial evaluated afatinib or placebo for patients who had previously received chemotherapy and a first-generation EGFR inhibitor, either erlotinib or gefitinib. No overall survival benefit was reported, the primary endpoint, and only 7% of the patients achieved a partial response on the afatinib arm (Miller 2012).

After the 2 months of afatinib, the patient was referred to me and received rociletinib on a clinical trial. She achieved a dramatic partial response on her first scan, and this has been maintained for about 10 months. However, she experienced hyperglycemia that is being well managed with metformin.

DR LOVE: What are your thoughts on the efficacy of the third-generation EGFR TKIs rociletinib and osimertinib (AZD9291) in the treatment of non-small cell lung cancer (NSCLC)?

DR SEQUIST: Both agents seem to be active in Phase I and Phase II studies, especially in patients with T790M mutations (1.1; 1.2). They are designed to hit both the activating mutations and the T790M EGFR mutations but not the wild-type form. Inhibition of wild-type EGFR causes the rash, diarrhea and nail changes observed with the older-generation inhibitors. The hyperglycemia associated with rociletinib in some patients can be managed with metformin. The response rate for both osimertinib and

1.1

AURA: A Phase I/II Trial of Osimertinib (AZD9291) for 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

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

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

1.2

Results of a Phase I/II Trial of Rociletinib (CO-1686) for Patients with EGFR Mutation-Positive 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

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

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

rociletinib is approximately 60% for patients with T790M-mutant disease (1.1; 1.2). I've administered osimertinib to several patients, and most have not experienced any side effects.

The ongoing Phase II/III TIGER-1 trial is investigating rociletinib versus erlotinib as first-line therapy for patients with EGFR mutation-positive advanced NSCLC (NCT02186301). Also, the ongoing Phase III FLAURA trial is assessing osimertinib versus erlotinib or gefitinib as first-line therapy for patients with EGFR-mutant advanced NSCLC (NCT02296125). I believe these agents will have a huge effect for patients when they're FDA approved.

Editor's note: Subsequent to this interview, on November 13, 2015, the FDA granted accelerated approval to osimertinib for patients with advanced EGFR T790M mutation-positive NSCLC after disease progression on a prior EGFR TKI.

DR LOVE: Do you see a role for afatinib/cetuximab in the treatment of advanced NSCLC?

DR SEQUIST: I would use this combination in the right situation, as it has a track record of activity. Afatinib alone is not active after acquired resistance to EGFR inhibitors, but when used in combination with cetuximab, a consistent response rate of 30% has been observed in a couple of different populations (Janjigian 2014). The caveat is that this combination can cause a significant amount of dermatologic toxicity.

The ongoing Phase II/III SWOG-S1403 trial is evaluating afatinib with or without cetuximab for patients with newly diagnosed advanced EGFR mutation-positive NSCLC (1.3). The hypothesis is that first-line use of the combination can yield a longer progression-free survival (PFS) versus single-agent afatinib.

1.3

SWOG-S1403: A Phase II/III Trial of Afatinib with or without Cetuximab in Treatment-Naïve Advanced EGFR-Mutant Non-Small Cell Lung Cancer (NSCLC)

Protocol ID: NCT02438722

Target accrual (N = 605)

- Newly diagnosed Stage IV or recurrent NSCLC
- EGFR mutation-positive disease
- Availability of tissue sample
- ECOG PS 0-2

R

- Afatinib
- Afatinib + cetuximab

Primary endpoint: Progression-free survival (Phase II); overall survival (Phase III)

www.clinicaltrials.gov. Accessed December 2015.

Tracks 9-10

DR LOVE: Would you discuss the design and results of the Phase II SELECT trial and the Phase III RADIANT trial of adjuvant erlotinib for patients with Stage I to Stage III NSCLC?

DR SEQUIST: The main issue with the SELECT trial design is that it was a single-arm study, so it is difficult to draw conclusions (Pennell 2014). One hundred patients enrolled on the trial, and all had EGFR mutation-positive disease. Patients received 2

years of adjuvant erlotinib. The trial data are mature and will soon be published. The 2-year disease-free survival (DFS) rate was 96%. So the number of patients with recurrent disease on treatment was low. Now that the patients have stopped the 2 years of adjuvant erlotinib, we've started to see more disease recurrence.

RADIANT was a prospective randomized trial that was not limited to patients with EGFR-mutant disease. However, a small proportion of patients had EGFR mutation-positive disease. Patients were randomly assigned to 2 years of adjuvant erlotinib versus placebo (Kelly 2015; [1.4]).

In the overall population of patients, the study demonstrated no significant difference in DFS. Because of the hierarchical testing procedure, if the overall analysis was negative, the investigators had no option to evaluate statistical significance in any of the patient subgroups. Even though the *p*-value was 0.039 for patients with EGFR mutation-positive disease, it did not translate to a statistically significant DFS advantage.

Hopefully, the ongoing randomized ALCHEMIST trial of erlotinib versus placebo will help shed more light on the appropriate treatment approach in terms of adjuvant therapy for patients with completely resected EGFR mutation-positive disease (NCT02193282). ■

1.4

RADIANT: Efficacy and Safety Results of a Phase III Trial of Adjuvant Erlotinib versus Placebo for Patients with Stage IB to IIIA Non-Small Cell Lung Cancer

Median DFS	Erlotinib	Placebo	Hazard ratio	*p*-value
All patients (n = 623, 350)	50.5 mo	48.2 mo	0.9	0.324
EGFR-mutant population (n = 102, 59)	46.4 mo	28.5 mo	0.61	0.039*
	Erlotinib (n = 611)		Placebo (n = 343)	
Select adverse events	All	Grade ≥3	All	Grade ≥3
Rash	86.4%	22.3%	32.1%	0.3%
Diarrhea	52.2%	6.2%	15.7%	0.3%
Pruritus	26.4%	1.3%	14.9%	0%
Fatigue	19.5%	0.8%	14.3%	0.9%
Dyspnea	14.6%	1.1%	18.1%	1.5%
Anorexia	13.1%	0.7%	7.0%	0.6%

* Not statistically significant because of the hierarchical testing procedure

Kelly K et al. *J Clin Oncol* 2015;33(34):4007-14.

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.

Kelly K et al. **Adjuvant erlotinib versus placebo in patients with stage IB-IIIA non-small-cell lung Cancer (RADIANT): A randomized, double-blind, phase III trial.** *J Clin Oncol* 2015;33(34):4007-14.

Miller VA et al. **Afatinib versus placebo for patients with advanced, metastatic non-small-cell lung cancer after failure of erlotinib, gefitinib, or both, and one or two lines of chemotherapy (LUX-Lung 1): A phase 2b/3 randomised trial.** *Lancet Oncol* 2012;13(5):528-38.

Pennell NA et al. **SELECT: A multicenter phase II trial of adjuvant erlotinib in resected early-stage EGFR mutation-positive NSCLC.** *Proc ASCO* 2014;**Abstract 7514**.

INTERVIEW

Gregory J Riely, MD, PhD

Dr Riely is Associate Attending at Memorial Sloan Kettering Cancer Center in New York, New York.

Tracks 1-17

Select Excerpts from the Interview

Tracks 2-3, 5, 8-9

DR LOVE: What is your experience with the next-generation ALK inhibitor ceritinib for patients with advanced NSCLC?

DR RIELY: Ceritinib was approved last year for the treatment of ALK-positive metastatic NSCLC after disease progression on or intolerance to crizotinib. Crizotinib

and ceritinib are similar, but the binding of ceritinib to ALK is much better. I believe that this is the reason why ceritinib is more effective in the brain.

The FDA-approved dose of ceritinib is 750 mg daily, which is quite high. The number of patients who receive that dose is small. I routinely start patients who are young and fit at 600 mg and may reduce the dose to 450 mg for older patients.

Gastrointestinal problems such as nausea and diarrhea are the biggest challenge in determining the right dose of ceritinib. The other major side effect is liver function test abnormalities, which we monitor and then adjust the dose if necessary.

DR LOVE: How would you sequence crizotinib and ceritinib for patients with ALK-positive NSCLC?

DR RIELY: Treatment for ALK-positive lung cancer with crizotinib in the first-line setting results in a median PFS of approximately 11 months. If ceritinib is administered after disease progression on crizotinib, the median PFS is around 7 months. Taken together, the median PFS for crizotinib and ceritinib is about 18 months. When ceritinib is administered as first-line therapy, the median PFS is about 10 months (Kim 2014).

So switching from one to the other does not necessarily yield optimal benefits. The reason for administering crizotinib first would be more related to drug tolerability. Patients tend to find crizotinib easier to tolerate than ceritinib. However, some patients who are receiving crizotinib may experience significant edema, which can be a real problem. An early switch to ceritinib for those patients who don't tolerate crizotinib well would be reasonable.

DR LOVE: What are your thoughts about continuing crizotinib beyond disease progression for ALK-positive NSCLC?

DR RIELY: No matter which agent we choose, most patients will eventually develop progressive disease. For ALK-positive NSCLC, I believe one should try to maximize the benefit from crizotinib. If single sites of disease progression are amenable to treatments such as radiation therapy, surgery or interventional radiology procedures, they should be employed as well. This will delay the start of the next PFS clock and the switch to systemic therapy.

DR LOVE: What is known about the activity and tolerability of alectinib for ALK-rearranged NSCLC?

DR RIELY: I believe that alectinib is the next agent that will become available for patients with ALK-positive NSCLC. Alectinib, similar to ceritinib, is a more potent ALK inhibitor than crizotinib.

Alectinib began its initial development in Japan. The first trial of alectinib in patients with crizotinib-naïve, ALK-positive disease reported an objective response rate of more than 90%. This was one of the highest response rates we've seen in the treatment of NSCLC. The dose used in that study was 300 mg. A later study by our group identified the recommended Phase II dose as 600 mg, double the dose used in the Japanese study (Gadgeel 2014). My experience with alectinib is that it's relatively well tolerated.

DR LOVE: How do patients with ALK-positive NSCLC respond to chemotherapy?

DR RIELY: Chemotherapy may be slightly more effective for patients with ALK-positive disease. Data from a randomized trial of cisplatin/pemetrexed versus

crizotinib as first-line therapy showed that the combination was effective. So that would be my treatment of choice. A study randomly assigning patients to standard chemotherapy or crizotinib in the second-line setting demonstrated that PFS was much better with pemetrexed than with docetaxel (Shaw 2013).

Track 10

DR LOVE: What is your approach to the use of bevacizumab with erlotinib for patients with advanced EGFR mutation-positive NSCLC?

DR RIELY: Results from a recent study demonstrated that combining bevacizumab with erlotinib in the first-line setting significantly improves PFS in comparison to erlotinib alone. It's a relatively small data set from Japan, but it does demonstrate that the addition of bevacizumab to erlotinib is efficacious (Seto 2014; [2.1]).

In practice, patient preferences influence my choice of therapy. Patients who want to spend as little time in the doctor's office as possible may choose single-agent erlotinib. Other patients want the best response or the longest duration of response and are happy to receive erlotinib with bevacizumab or investigate clinical trial options.

2.1

Results of a Phase II Trial of Erlotinib Alone or with Bevacizumab (Bev) as First-Line Therapy for Patients with Advanced EGFR-Mutant Nonsquamous Non-Small Cell Lung Cancer

Efficacy	Erlotinib + bev (n = 75)	Erlotinib (n = 77)	Hazard ratio	*p*-value
Median PFS	16.0 mo	9.7 mo	0.54	0.0015
ORR	69%	64%	NR	0.49
DCR	99%	88%	NR	0.0177
	Erlotinib + bev (n = 75)		Erlotinib (n = 77)	
Select adverse events	All	Grade 3 or 4	All	Grade 3 or 4
Rash	99%	25%	99%	19%
Diarrhea	81%	1%	78%	1%
Hemorrhagic event	72%	3%	29%	0%
Hypertension	76%	60%	13%	10%
Proteinuria	52%	8%	4%	0%

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

Seto T et al. *Lancet Oncol* 2014;15(11):1236-44.

Tracks 14-15

DR LOVE: Ramucirumab, an antibody against VEGFR2, was recently approved for use in combination with docetaxel for patients with metastatic NSCLC with disease progression after platinum-based therapy. Would you discuss the results of the study that led to its approval and your approach in practice?

DR RIELY: A substantial amount of data now indicate that ramucirumab improves PFS, overall survival and response rate in the second-line setting in combination with

docetaxel, though the improvement is not dramatic (Garon 2014; [2.2]). The adverse effects associated with ramucirumab are modest. So it would be a reasonable option for patients who do not have EGFR or ALK mutations and for whom second-line docetaxel is being considered.

I administer ramucirumab for my patients occasionally. Because the clinical benefit is marginal, we must consider the cost, side effects and convenience of administration. As a member of the NCCN Guidelines Panel, I must consider these factors when developing treatment recommendations. In my practice I consider everything I can to help my patients live longer and maintain better control of their disease. ■

2.2

REVEL: Results of a Phase III Trial of Docetaxel (Doc) with or without Ramucirumab (Ram) as Second-Line Therapy for Patients with Stage IV Non-Small Cell Lung Cancer After Disease Progression on 1 Platinum-Based Regimen

Efficacy	Ram + doc (n = 628)	Plac + doc (n = 625)	Hazard ratio	*p*-value
Median OS	10.5 mo	9.1 mo	0.86	0.023
Median PFS	4.5 mo	3.0 mo	0.76	<0.0001
ORR	23%	14%	1.89*	<0.0001
DCR	64%	53%	1.60*	<0.0001

	Ram + doc (n = 627)		Plac + doc (n = 618)	
Select adverse events	**All**	**Grade 3 or 4**	**All**	**Grade 3 or 4**
Neutropenia	55%	49%	45%	39%
Febrile neutropenia	16%	16%	10%	10%
Bleeding/hemorrhage	29%	2%	15%	2%
Hypertension	11%	6%	5%	2%
Venous thromboembolism	3%	2%	6%	3%

Plac = placebo; OS = overall survival; PFS = progression-free survival; ORR = objective response rate; DCR = disease control rate

* Odds ratio

Garon EB et al. *Lancet* 2014;384(9944):665-73.

SELECT PUBLICATIONS

Gadgeel SM et al. **Safety and activity of alectinib against systemic disease and brain metastases in patients with crizotinib-resistant ALK-rearranged non-small-cell lung cancer (AF-002JG): Results from the dose-finding portion of a phase 1/2 study.** *Lancet Oncol* 2014;15(10):1119-28.

Garon EB et al. **Ramucirumab plus docetaxel versus placebo plus docetaxel for second-line treatment of stage IV non-small-cell lung cancer after disease progression on platinum-based therapy (REVEL): A multicentre, double-blind, randomised phase 3 trial.** *Lancet* 2014;384(9944):665-73.

Kim DW et al. **Ceritinib in advanced anaplastic lymphoma kinase (ALK)-rearranged (ALK+) non-small cell lung cancer (NSCLC): Results of the ASCEND-1 trial.** *Proc ASCO* 2014;**Abstract 8003**.

Seto T et al. **Erlotinib alone or with bevacizumab as first-line therapy in patients with advanced non-squamous non-small-cell lung cancer harbouring EGFR mutations (JO25567): An open-label, randomised, multicentre, phase 2 study.** *Lancet Oncol* 2014;15(11):1236-44.

Shaw AT et al. **Crizotinib versus chemotherapy in advanced ALK-positive lung cancer.** *N Engl J Med* 2013;368(25):2385-94.

INTERVIEW

Sarah B Goldberg, MD, MPH

Dr Goldberg is Assistant Professor of Medicine at Yale Cancer Center in New Haven, Connecticut.

Tracks 1-16

Select Excerpts from the Interview

Tracks 1, 5, 13

DR LOVE: Would you discuss your perspective on the rapidly emerging role of checkpoint inhibitors in the treatment of lung cancer?

DR GOLDBERG: The initial approvals of nivolumab and pembrolizumab were in melanoma, but now the PD-1 and PD-L1 inhibitors are being developed for multiple cancer types, and we're seeing astonishing Phase III data with some of these agents.

Nivolumab was recently approved for patients with squamous cell lung cancer on the basis of a trial comparing that antibody to docetaxel in the second-line setting after disease progression on a platinum-based doublet (Brahmer 2015; [3.1]). At ASCO this year we heard the results of a similar trial that enrolled patients with nonsquamous cell lung cancer, and again the data are promising with a survival benefit, but nivolumab has not yet been approved in that setting (Paz-Ares 2015; [3.2]).

Editor's note: Subsequent to this interview, on October 2, 2015, the FDA granted accelerated approval to pembrolizumab for patients with previously treated metastatic NSCLC with PD-L1 expression. On October 9, 2015, the FDA expanded approval for nivolumab to include patients with metastatic nonsquamous NSCLC and disease progression during or after platinum-based chemotherapy.

DR LOVE: What kind of response rate, duration of response and side effects have been observed with anti-PD-1 antibodies?

DR GOLDBERG: The response rates are better with nivolumab than with docetaxel, but they're still lower than many people would like, at approximately 20%. The duration of response is exciting, with many patients living several years, and this is in the setting of heavily pretreated disease.

Another astonishing feature of these agents is that many patients experience no or limited toxicity. The potential challenge is that when patients do develop toxicity, it can be in the form of side effects that we typically don't see, including endocrinopathies like thyroid dysfunction and adrenal insufficiency. I recently saw a patient who was experiencing nonspecific symptoms, was fatigued and was not eating well. It was

3.1

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 Regimen

Outcome	Nivolumab (n = 135)	Docetaxel (n = 137)	Hazard ratio	*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
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%
Nausea	9%	0%	23%	2%
Diarrhea	8%	0%	20%	2%
Pneumonitis	5%	0%	0%	0%
Arthralgia	5%	0%	7%	0%
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; PN = peripheral neuropathy * Odds ratio: 2.6

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

3.2

CheckMate 057: Efficacy Results of a Phase III Trial of Nivolumab versus Docetaxel in Advanced Nonsquamous Non-Small Cell Lung Cancer

	Nivolumab (n = 292)	Docetaxel (n = 290)	Hazard ratio	*p*-value
Median OS	12.2 months	9.4 months	0.73	0.002
Median PFS	2.3 months	4.2 months	0.92	0.3932
ORR*	56 (19%)	36 (12%)	—	0.02
Complete response	4 (1%)	1 (<1%)	—	—
Partial response	52 (18%)	35 (12%)	—	—
Stable disease	74 (25%)	122 (42%)	—	—
Median time to response	2.1 months	2.6 months	—	—
Median duration of response	17.2 months	5.6 months	—	—

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

* Odds ratio = 1.72

Paz-Ares L et al. *Proc ASCO* 2015;**Abstract LBA109**; Borghaei H et al. *N Engl J Med* 2015;373(17):1627-39.

a notable difference from only a few weeks before, and her cortisol level was undetectable. You need to keep this in mind because it's so different than with chemotherapy. Checking a patient's cortisol level is not something we usually consider doing.

Pneumonitis, hepatitis and colitis have been problematic in some patients. Now that we are more aware that pneumonitis is a potentially life-threatening issue, we've become aggressive in testing for it even if it's only a remote possibility and then treating it with steroids.

Colitis is less common than it is with the anti-CTLA-4 antibodies, but it's possible, especially when we start combining different immunotherapies. Any organ system can be affected by these agents. Some patients develop skin toxicities, although these are manageable with oral steroids or IV steroids in certain cases.

DR LOVE: Do you stop treatment with a PD-1 or PD-L1 inhibitor after a certain period? Have you seen patients who stopped treatment on a trial and demonstrated continued responses?

DR GOLDBERG: The first question does not have an answer yet. Some patients on trials receive treatment for 1 year and then stop, and many trials allow re-treatment at disease progression. Some trials administer treatment for 2 years and then stop, and still others use continuous treatment until disease progression or toxicity. So it's unclear how long to administer treatment off trial.

We do see patients with sustained responses. In the trials that require stopping treatment after 1 or 2 years, several patients have continued to demonstrate responses for years after. But it's too early to know the right duration of treatment. With such minimal toxicity, it's tempting to continue treatment, but then the issue of cost arises.

These drugs are expensive. Do you continue treatment forever even if someone might experience a sustained benefit without it? Hopefully, with more data we will understand what's happening after treatment is stopped and whether rechallenging after disease progression is beneficial.

DR LOVE: What do we know about anti-PD-L1 antibodies and how they compare to anti-PD-1 antibodies?

DR GOLDBERG: In many ways the mechanisms of action of anti-PD-1 and anti-PD-L1 antibodies are similar. By inhibiting either the ligand or the receptor, you're preventing the interaction between PD-1 and PD-L1. But because the immune system is complicated, other interactions are also being inhibited by each agent, and that's where the potential differences in benefit and toxicity come into play.

We're starting to learn more about the anti-PD-L1 antibodies, such as atezolizumab, but the trials are not as far along as those with the anti-PD-1 antibodies. The data appear promising (Spira 2015; [3.3]), although it is difficult to distinguish whether one agent is better than another. They do seem to be tolerable — based on the biology of the immune system, perhaps even more tolerable than the anti-PD-1 antibodies, but it is difficult to draw conclusions from the trials. ■

3.3

POPLAR: A Randomized Phase II Study Comparing Atezolizumab (MPDL3280A) to Docetaxel for Previously Treated Advanced Non-Small Cell Lung Cancer

Outcome	Atezolizumab (n = 144)	Docetaxel (n = 143)	Hazard ratio	*p*-value
Median OS	11.4 mo	9.5 mo	0.77	0.11
TC3 or IC3 (n = 24, 23)	NR	11.1 mo	0.46	0.070
TC2/3 or IC2/3 (n = 50, 55)	13 mo	7.4 mo	0.56	0.026
TC1/2/3 or IC1/2/3 (n = 93, 102)	NR	9.1 mo	0.63	0.024
TC0 and IC0 (n = 51, 41)	9.7 mo	9.7 mo	1.12	0.70
Median PFS	2.8 mo	3.4 mo	0.98	—
ORR	15%	15%	—	—
Safety summary	**Atezolizumab** (n = 142)		**Docetaxel** (n = 135)	
Median treatment duration	3.7 mo		2.1 mo	
All-grade AEs, any cause	97%		96%	
Grade 3-4 AEs, any cause	39%		52%	
Withdrawal from treatment due to AEs	8%		22%	

OS = overall survival; TC3 or IC3 = tumor cells ≥50% or immune cells ≥10% PD-L1-positive; NR = not reached; TC2/3 or IC2/3 = TC or IC ≥5% PD-L1-positive; TC1/2/3 or IC1/2/3 = TC or IC ≥1% PD-L1-positive; TC0 and IC0 = TC and IC <1% PD-L1-positive; PFS = progression-free survival; ORR = overall response rate; AEs = adverse events

With atezolizumab, immune-related AEs included increased AST (4%), increased ALT (4%), pneumonitis (2%), colitis (1%) and hepatitis (1%).

Spira AI et al. *Proc ASCO* 2015;**Abstract 8010**.

SELECT PUBLICATIONS

Brahmer J et al. **Nivolumab versus docetaxel in advanced squamous-cell non–small-cell lung cancer.** *N Engl J Med* 2015;373(2):123-35.

Spira AI et al. **Efficacy, safety and predictive biomarker results from a randomized phase II study comparing MPDL3280A vs docetaxel in 2L/3L NSCLC (POPLAR).** *Proc ASCO* 2015;**Abstract 8010**.

INTERVIEW

Ronald B Natale, MD

Dr Natale is Director of the Lung Cancer Clinical Research Program and Acting Director of the Phase I Clinical Trials Unit at the Samuel Oschin Comprehensive Cancer Institute at Cedars-Sinai Medical Center in Los Angeles, California.

Tracks 1-8

Track 1 **Case discussion:** A 52-year-old man and never smoker with EGFR L858R mutation-positive Stage IIIA adenocarcinoma of the lung receives adjuvant erlotinib on the RADIANT trial

Track 2 Use of next-generation sequencing in patients with recurrent adenocarcinoma of the lung

Track 3 Clinical trial of carboplatin/gemcitabine in combination with the PARP inhibitor iniparib

Track 4 Activity of third-generation EGFR TKIs in patients with T790M-mutant NSCLC

Track 5 Dose, schedule and activity of nanoparticle albumin-bound (*nab*) paclitaxel with carboplatin for untreated locally advanced or metastatic NSCLC

Track 6 Use of gemcitabine as second-line therapy for pan-wild-type adenocarcinoma of the lung

Track 7 Therapeutic options for patients with advanced adenocarcinoma of the lung who are eligible to receive bevacizumab

Track 8 Perspective on the activity of ramucirumab with docetaxel as second-line therapy for Stage IV NSCLC

Select Excerpts from the Interview

Track 5

CASE DISCUSSION: A 62-year-old woman with advanced adenocarcinoma of the lung achieves a good response with carboplatin/paclitaxel/bevacizumab but experiences severe paclitaxel-associated side effects

DR NATALE: This was a fairly healthy patient who stopped smoking about 20 years ago. Her tumor had no detectable mutations. A medical oncologist in the community administered induction therapy with carboplatin/paclitaxel/bevacizumab, and the patient experienced a terrific response.

She came to see me during treatment because she was extraordinarily sensitive to paclitaxel and developed significant problems with peripheral neuropathy. This patient also had severe hematologic toxicity, which was more than what is usually observed with carboplatin/paclitaxel. She developed thrombocytopenia and had been hospitalized because of febrile neutropenia. I talked with her oncologist regarding trying different schedules of administration and alternating with docetaxel.

DR LOVE: *Nab* paclitaxel is approved in lung cancer in combination with carboplatin for patients with untreated locally advanced or metastatic NSCLC. What is your view on its efficacy and tolerability?

DR NATALE: *Nab* paclitaxel is well tolerated when it's administered on a weekly basis. It is an available option, but I don't administer it often. A study by Belani and colleagues comparing carboplatin/paclitaxel every 3 weeks to a weekly schedule in patients with advanced NSCLC showed no significant difference in efficacy between the 2 arms. Less neuropathy but more anemia was evident on the weekly carboplatin/paclitaxel arm (Belani 2008).

A subsequent study comparing weekly *nab* paclitaxel with carboplatin to every 3-week carboplatin/paclitaxel demonstrated a higher response rate and an insignificant improvement in PFS with *nab* paclitaxel/carboplatin and no difference in overall survival. The differences in toxicity included less neuropathy with *nab* paclitaxel but a higher incidence of anemia requiring erythropoietic growth factors or blood transfusions (4.1). The results were similar to the earlier study by Belani and colleagues.

From my perspective, weekly *nab* paclitaxel, despite good efficacy, is not attractive because of its cost. I'm an outlier in this respect. For many oncologists, *nab* paclitaxel is the go-to agent, especially for elderly patients. I understand their rationale. It is FDA approved and effective.

4.1

Phase III Trial of *Nab* Paclitaxel/Carboplatin (*Nab*-PC) versus Solvent-Based Paclitaxel/Carboplatin (sb-PC) as First-Line Therapy for Patients with Advanced Non-Small Cell Lung Cancer

Efficacy	*Nab*-PC		sb-PC		*p*-value
Overall response rate					
All patients (n = 521, 531)	33%		25%		0.005
Squamous (n = 229, 221)	41%		24%		<0.001
Nonsquamous (n = 292, 310)	26%		25%		0.808
Patients aged ≥70 y (n = 74, 82)	34%		24%		0.196
Median progression-free survival					
All patients (n = 521, 531)	6.3 mo		5.8 mo		0.214
Squamous (n = 229, 221)	5.6 mo		5.7 mo		0.245
Nonsquamous (n = 292, 310)	6.9 mo		6.5 mo		0.532
Patients aged ≥70 y (n = 74, 82)	8.0 mo		6.8 mo		0.134
Median overall survival					
All patients (n = 521, 531)	12.1 mo		11.2 mo		0.271
Squamous (n = 229, 221)	10.7 mo		9.5 mo		0.284
Nonsquamous (n = 292, 310)	13.1 mo		13.0 mo		0.611
Patients aged ≥70 y (n = 74, 82)	19.9 mo		10.4 mo		0.009
Select adverse events	Grade 3	Grade 4	Grade 3	Grade 4	*p*-value
Neutropenia	33%	14%	32%	26%	<0.001
Anemia	22%	5%	6%	<1%	<0.001
Thrombocytopenia	13%	5%	7%	2%	<0.001
Sensory neuropathy	3%	0%	11%	<1%	<0.001

Socinski MA et al. *Ann Oncol* 2013;24(9):2390-6; Socinski MA et al. *Ann Oncol* 2013;24(2):314-21; Socinski MA et al. *J Clin Oncol* 2012;30(17):2055-62.

Tracks 7-8

DR LOVE: What's your usual up-front induction treatment for metastatic wild-type adenocarcinoma, and how do you approach maintenance therapy?

DR NATALE: My choice for first-line therapy for patients with nonsquamous histology is carboplatin/pemetrexed, usually without bevacizumab. However, for younger patients I add bevacizumab to carboplatin/pemetrexed to maximize benefit. More importantly, in younger patients the adverse effects of adding bevacizumab would be less than in an older patient population. When I administer carboplatin/pemetrexed in the first-line setting, I usually continue maintenance therapy with pemetrexed.

The NCCN Guidelines allow the addition of bevacizumab to any platinum doublet as induction therapy. Unfortunately, the only studies showing a positive outcome with bevacizumab in the first-line setting are those combining it with carboplatin/paclitaxel (Zhou 2015). So in the absence of data that show that adding bevacizumab to carboplatin/pemetrexed in the first-line setting improves outcome, I prefer not to add bevacizumab.

DR LOVE: What is your preference for therapy for these patients in the second-line setting outside a clinical trial?

DR NATALE: Docetaxel is FDA approved and is the gold standard against which all other regimens in the second-line setting are compared. So outside a protocol setting, docetaxel remains my first choice for patients who previously received carboplatin and pemetrexed.

DR LOVE: Would you comment on the findings from the Phase III REVEL trial evaluating docetaxel with or without the addition of ramucirumab in the second-line treatment of Stage IV NSCLC after disease progression on 1 platinum-based chemotherapy regimen?

DR NATALE: The REVEL trial demonstrated a small benefit with the addition of ramucirumab to docetaxel as second-line therapy for metastatic NSCLC (Garon 2014). My experience with adding ramucirumab to docetaxel in this setting has been limited to a few patients. I administer docetaxel to most of my patients. But for young, healthy patients who have a good performance status, adding ramucirumab to docetaxel is a good option. ■

SELECT PUBLICATIONS

Belani C et al. **Randomized, Phase III study of weekly paclitaxel in combination with carboplatin versus standard every-3-weeks administration of carboplatin and paclitaxel for patients with previously untreated advanced non-small-cell lung cancer.** *J Clin Oncol* 2008;26(3):468-73.

Garon EB et al. **Ramucirumab plus docetaxel versus placebo plus docetaxel for second-line treatment of stage IV non-small-cell lung cancer after disease progression on platinum-based therapy (REVEL): A multicentre, double-blind, randomised phase 3 trial.** *Lancet* 2014;384(9944):665-73.

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.

Socinski MA et al. **Safety and efficacy analysis by histology of weekly *nab*-paclitaxel in combination with carboplatin as first-line therapy in patients with advanced non-small-cell lung cancer.** *Ann Oncol* 2013;24(9):2390-6.

Socinski MA et al. **Safety and efficacy of weekly *nab*-paclitaxel in combination with carboplatin as first-line therapy in elderly patients with advanced non-small-cell lung cancer.** *Ann Oncol* 2013;24(2):314-21.

Zhou C et al. **BEYOND: A randomized, double-blind, placebo-controlled, multicenter, Phase III study of first-line carboplatin/paclitaxel plus bevacizumab or placebo in Chinese patients with advanced or recurrent nonsquamous non-small-cell lung cancer.** *J Clin Oncol* 2015;33(19):2197-204.

QUESTIONS (PLEASE CIRCLE ANSWER):

1. **Phase I/II trials evaluating the efficacy of osimertinib (AZD9291) and rociletinib (CO-1686) for patients with EGFR mutation-positive advanced NSCLC demonstrated higher efficacy among patients with _____.**

   a. EGFR T790M mutation-positive disease
   b. EGFR T790M mutation-negative disease

2. **The ongoing Phase II/III SWOG-S1403 trial is investigating afatinib with or without _____ for patients with newly diagnosed advanced EGFR mutation-positive NSCLC.**

   a. Rociletinib
   b. Osimertinib
   c. Cetuximab

3. **A study by Socinski and colleagues evaluating *nab* paclitaxel/carboplatin versus solvent-based paclitaxel/carboplatin as first-line therapy for patients with advanced NSCLC demonstrated an increase in the incidence of _____ on the *nab* paclitaxel arm.**

   a. Neutropenia
   b. Anemia
   c. Sensory neuropathy
   d. All of the above
   e. Both a and b

4. **The results of the Phase III REVEL trial of second-line docetaxel with or without ramucirumab for patients with Stage IV NSCLC after disease progression on a platinum-based regimen demonstrated a statistically significant improvement in _____ with the addition of ramucirumab to docetaxel.**

   a. Median overall survival
   b. Median PFS
   c. Overall response rate
   d. Disease control rate
   e. Both a and c
   f. All of the above

5. **A Phase II trial of erlotinib alone or with bevacizumab as first-line therapy for patients with advanced EGFR-mutant nonsquamous NSCLC did not demonstrate a statistically significant improvement in median PFS with the addition of bevacizumab.**

   a. True
   b. False

6. **Which of the following ALK inhibitors is FDA approved for the treatment of ALK-positive metastatic NSCLC?**

   a. Crizotinib
   b. Ceritinib
   c. Alectinib
   d. Both a and b
   e. All of the above

7. **Data from the CheckMate 017 trial in previously treated advanced squamous NSCLC indicated a statistically significant improvement in median overall survival among patients who received nivolumab compared to those who received docetaxel.**

   a. True
   b. False

8. **Data from the Phase III CheckMate 057 trial of nivolumab versus docetaxel for patients with advanced nonsquamous NSCLC after disease progression on platinum-based doublet therapy demonstrated a statistically significant improvement in _____ with nivolumab therapy.**

   a. Median overall survival
   b. Median PFS
   c. Overall response rate
   d. Both a and b
   e. Both a and c

9. **Data from the POPLAR trial for patients with previously treated, advanced NSCLC demonstrated a pattern of improved survival with _____ compared to docetaxel, correlating with increased levels of PD-L1 expression.**

   a. Pembrolizumab
   b. Atezolizumab
   c. Nivolumab

10. **The Phase III PointBreak trial evaluating carboplatin/paclitaxel/bevacizumab followed by bevacizumab maintenance therapy versus carboplatin/pemetrexed/bevacizumab followed by pemetrexed/bevacizumab maintenance therapy for patients with advanced nonsquamous NSCLC demonstrated a statistically significant difference in overall survival between the 2 arms.**

    a. True
    b. False

EDUCATIONAL ASSESSMENT AND CREDIT FORM

Lung Cancer Update — Issue 2, 2015

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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
Activity and safety of new strategies (third-generation TKIs rociletinib and osimertinib) 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
Erlotinib and bevacizumab as first-line therapy for advanced EGFR mutation-positive nonsquamous 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
Available efficacy and safety data with anti-PD-1/PD-L1 antibodies for patients with squamous and nonsquamous NSCLC compared to docetaxel for patients with advanced NSCLC with disease progression on or after platinum-based chemotherapy	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).

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☐ 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

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

- 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. . . . 4 3 2 1 N/M N/A
- Integrate newly approved agents for treatment in second- or later-line settings. . . . . 4 3 2 1 N/M N/A
- Formulate an approach to incorporate newly approved checkpoint inhibitors into the treatment algorithm for patients with metastatic NSCLC. . . . . 4 3 2 1 N/M N/A
- Employ an understanding of next-generation sequencing, and determine its clinical and/or research applicability 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 options in this setting. . . . . 4 3 2 1 N/M N/A
- Identify distinct subtypes of adenocarcinoma of the lung — including those with EGFR mutations, EML4-ALK gene fusions, ROS1 gene rearrangements and other recently identified driver mutations — and the approved and investigational treatment options for patients with these genetic abnormalities. . . . . 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?

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.....

.....

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

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Lecia V Sequist, MD, MPH	4 3 2 1	4 3 2 1
Gregory J Riely, MD, PhD	4 3 2 1	4 3 2 1
Sarah B Goldberg, MD, MPH	4 3 2 1	4 3 2 1
Ronald B Natale, 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:

.....

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