

Lung Cancer™

U P D A T E

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

FACULTY INTERVIEWS

Alexander E Drilon, MD
John V Heymach, MD, PhD
Jean-Charles Soria, MD, PhD
Martin Reck, MD, PhD

EDITOR

Neil Love, MD

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2 Audio CDs
Monograph

CME
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Lung Cancer Update

A Continuing Medical Education Audio Series

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

- Recall the scientific rationale for ongoing investigation of novel agents or immunotherapeutic approaches in lung cancer, and counsel appropriately selected patients about study participation.
- Assess available research evidence with existing and emerging therapeutic options for patients with advanced squamous cell carcinoma of the lung, and use this information to guide clinical care and protocol opportunities for these individuals.
- Employ an understanding of next-generation sequencing, and 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 use this information to develop optimal therapeutic approaches.
- Formulate a plan to incorporate checkpoint inhibitor therapy into the treatment of advanced non-small cell lung cancer and subsequently monitor immune-related side effects when they occur.

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EDITOR



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INTERVIEW

Alexander E Drilon, MD

Dr Drilon is Assistant Attending Physician in the Thoracic Oncology Service and Developmental Therapeutics Group at Memorial Sloan Kettering Cancer Center in New York, New York.

Tracks 1-15

- Track 1 Case discussion:** A 45-year-old woman and never smoker with metastatic adenocarcinoma of the lung for whom a next-generation sequencing (NGS) assay identifies a RET rearrangement
- Track 2** Use of NGS to identify actionable genomic alterations in patients with adenocarcinoma of the lung otherwise negative for such alterations by other genomic testing
- Track 3** Identification of actionable mutations in patients with squamous cell carcinoma (SCC) of the lung
- Track 4** Integration of NGS technologies into clinical practice
- Track 5** Activity of pemetrexed-based systemic therapy in RET-rearranged non-small cell lung cancer (NSCLC)
- Track 6** Results of a Phase II trial of cabozantinib for patients with advanced RET-rearranged NSCLC
- Track 7** Perspective on the investigation of RET inhibitors approved for other solid tumors
- Track 8** Cabozantinib-associated transaminitis and hypopigmentation
- Track 9 Case discussion:** An 81-year-old woman and never smoker with previously treated recurrent adenocarcinoma of the lung receives crizotinib after NGS identifies a MET exon 14 mutation
- Track 10 Case discussion:** A 57-year-old man and current smoker with BRAF V600E mutation-positive adenocarcinoma of the lung and multiple brain metastases receives dabrafenib monotherapy after postoperative whole brain radiation therapy
- Track 11** Activity of dabrafenib alone and in combination with trametinib for patients with BRAF V600E mutation-positive NSCLC
- Track 12 Case discussion:** A 50-year-old woman and never smoker with previously treated metastatic adenocarcinoma of the lung is found to harbor a ROS1 rearrangement and experiences a durable partial response with crizotinib
- Track 13** Response to cabozantinib in advanced ROS1-rearranged adenocarcinoma
- Track 14 Case discussion:** A 63-year-old woman and former smoker with recurrent adenocarcinoma of the lung who is found to harbor a HER2 (ERBB2 L755S) point mutation receives neratinib on a clinical trial
- Track 15** Clinical experience with HER2-directed therapies for patients with HER2 mutation-positive adenocarcinoma of the lung

Select Excerpts from the Interview

Tracks 2-4

- ▶ **DR LOVE:** Would you discuss your recent paper on the use of next-generation sequencing (NGS) to identify actionable genomic alterations in patients with adenocarcinoma of the lung?

► **DR DRILON:** The premise of this paper was to determine how good NGS is as a clinical assay. We enrolled patients with lung adenocarcinoma who were never smokers or light smokers and who had tested negative for alterations in 11 genes, including EGFR, ALK and BRAF, via non-NGS methods. This was a unique population of patients chosen with the intent of trying to enrich the results for potential driver mutations. A broad, hybrid, capture-based NGS was performed on their tumor specimens.

Interestingly, in about 94% of patients who had “pan-negative” disease, a genomic alteration was identified by NGS. Findings included an EGFR mutation and several fusions, including ALK, RET and ROS1. It is difficult to explain why these mutations were not detected by non-NGS methods. NGS detected a driver mutation in 1 out of 4 of these patients for which a targeted therapy was listed in the NCCN Guidelines. We were able to administer targeted therapy to a portion of these patients, and they experienced responses.

In 39% of patients, NGS identified a genomic alteration with a targeted agent available on a clinical trial (Drilon 2015a; [1.1]). A lot of guidance must be provided to clinicians as to which genomic alterations are potentially actionable and for which alterations we might have targeted therapies that are approved or available on protocols.

► **DR LOVE:** What is the likelihood of finding a targetable mutation in squamous cell non-small cell lung cancer (NSCLC)?

► **DR DRILON:** We published a review in *Lancet Oncology* evaluating actionable alterations in squamous cell lung cancer, and several are recognized (Drilon 2012). About 1 out of 5 patients harbors an FGFR1 amplification. Other mutations, such as PIK3CA, PTEN and AKT, are enriched in squamous cell lung cancer. DDR2 mutations are another example, for which dasatinib has been described as a potentially useful agent.

► **DR LOVE:** Should oncologists in general practice be using NGS for patients with metastatic lung cancer?

► **DR DRILON:** I would definitely recommend that community oncologists use NGS as opposed to non-NGS methods. With NGS, we are able to identify many more clinically actionable genomic alterations for which targeted therapies are either approved or are in testing. Also, patients who undergo multiple non-NGS tests endure a huge biopsy load. In our study, two thirds of the patients required multiple biopsies.

Although the population chosen for the study included patients who were light/never smokers with adenocarcinoma, the results of the paper are applicable to patients with a

1.1

Next-Generation Sequencing (NGS) Identifies Actionable Genomic Alterations in Lung Adenocarcinomas Otherwise Negative for Such Alterations by Other Genomic Testing Approaches

“One or more genomic alterations were uncovered by NGS in tumors from 94% (n = 29 of 31) of patients. Actionable genomic alterations with a targeted agent based on NCCN Guidelines were identified in 26% of patients. Comprehensive genomic profiling using this method also identified a genomic alteration with a targeted agent available on a clinical trial in an additional 39% of patients.

These findings support first-line profiling of lung adenocarcinomas using this approach as a more comprehensive and efficient strategy compared with non-NGS testing.”

Drilon A et al. *Clin Cancer Res* 2015a;21(16):3631-9.

smoking history and to those with varied clinical features, including squamous cell carcinomas (SCC) and potentially other cancers of the lung, such as small cell lung cancer.

At our institution, we usually send tumor samples solely for NGS unless the patient is extremely symptomatic. NGS is wonderful in that it can capture 200 to 400 different genes, but the turnaround time is about 4 weeks. If you have a young patient who is a never smoker and you're suspicious that he or she may have an EGFR mutation or an ALK fusion, it is possible to conduct tests that have a quick turnaround time.

Tracks 5-6, 8

- ▶ **DR LOVE:** At ASCO 2015 you presented data from a Phase II study of cabozantinib for patients with advanced RET-rearranged lung cancer. Would you discuss the efficacy and side effects of cabozantinib in that study?

 - ▶ **DR DRILON:** The first stage of this Phase II trial has been completed. The overall response rate was approximately 40%, and the disease control rate was almost 100%. So no primary disease progression occurred. The progression-free survival (PFS) with cabozantinib was 7 months, and the median overall survival (OS) was 10 months (Drilon 2015b; [1.2]).
- Even though RET is a driver mutation, we observed responses in only 40% of patients. This may be speaking to the biology of RET rearrangements. It may be that we can elicit a 60% to 80% response rate using targeted therapy for one biologic “bucket” that includes EGFR mutations and ALK fusions, whereas another bucket, which consists of BRAF mutations and RET, responds with lower efficacy to single-agent targeted therapy. The flip side is that we also may need a better targeted agent. Many patients on this trial required dose reductions during therapy. Patients receiving cabozantinib may develop transaminitis. Another interesting side effect observed with chronic daily dosing of cabozantinib is hypopigmentation of the skin and the hair. In the future, it may be possible to discover a RET-specific inhibitor without a lot of off-target effects.
- ▶ **DR LOVE:** Would you also comment on your study investigating pemetrexed-based systemic therapy in RET-rearranged NSCLC?

1.2 Phase II Trial of Cabozantinib for Patients with Advanced RET-Rearranged Non-Small Cell Lung Cancer		
Efficacy	(n = 16)	
Overall response rate	6 (38%)	
Stable disease	9 (56%)	
Median progression-free survival	7 mo	
Median overall survival	10 mo	
Select adverse events	All grades	Grade 3
ALT increase	15 (94%)	0
AST increase	12 (75%)	1 (6%)
Diarrhea	10 (63%)	0
Skin/hair hypopigmentation	7 (44%)	0

Drilon A et al. *Proc ASCO 2015b*; **Abstract 8007**.

► **DR DRILON:** We presented data at the 2015 World Lung meeting showing that RET-rearranged lung cancer, like ALK-rearranged cancer, is sensitive to pemetrexed-based therapies (Delasos 2015). This retrospective analysis demonstrated a response rate of approximately 48% to pemetrexed-based systemic therapy in RET-rearranged lung cancer.

Track 11

► **DR LOVE:** What are your thoughts on the efficacy of the dabrafenib/trametinib combination for BRAF V600E mutation-positive NSCLC?

► **DR DRILON:** Data presented last year on single-agent dabrafenib in a Phase II study showed that the response rate was approximately 30%. However, we know from the melanoma experience that treatment of BRAF-mutant tumors with the combination of a BRAF and MEK inhibitor improves response rates.

At ASCO 2015, a Phase II trial demonstrated that patients with BRAF-mutant lung adenocarcinomas who received the combination of the BRAF inhibitor dabrafenib and the MEK inhibitor trametinib experienced a response rate of approximately 60%, echoing what is observed in melanoma (Planchard 2015; [1.3]).

Two patients at our institution with BRAF V600E mutations received single-agent BRAF inhibition. After disease progression, a MEK inhibitor was added. Both of these patients again responded to the combination with several months of disease control. So it's possible that if you come in with a BRAF inhibitor at disease progression, you might be able to yield more efficacy with the addition of a MEK inhibitor. ■

1.3

Interim Results of a Phase II Study of the BRAF Inhibitor Dabrafenib in Combination with the MEK Inhibitor Trametinib in Patients with BRAF V600E-Mutated Metastatic Non-Small Cell Lung Cancer

Efficacy	Dabrafenib + trametinib (n = 24)	
	Overall response rate	15 (63%)
Disease control rate (>12 wk)	88%	
	(n = 33)	
Select adverse events	All grades	Grade ≥3
Pyrexia	13 (39%)	1 (3%)
Diarrhea	11 (33%)	1 (3%)
Nausea	11 (33%)	0
Vomiting	11 (33%)	0
Rash	7 (21%)	1 (3%)
Asthenia	7 (21%)	0
Peripheral edema	7 (21%)	0

Planchard D et al. *Proc ASCO 2015*; **Abstract 8006**.

SELECT PUBLICATIONS

Delasos L et al. **Clinical outcomes with pemetrexed-based systemic therapy in RET-rearranged lung cancers.** *Proc IASLC 2015*; **Abstract 03.05**.

Drilon A et al. **Squamous-cell carcinomas of the lung: Emerging biology, controversies, and the promise of targeted therapy.** *Lancet Oncol 2012*;13(10):e418-26.



INTERVIEW

John V Heymach, MD, PhD

Dr Heymach is Professor and Chair of Thoracic/Head and Neck Medical Oncology at The University of Texas MD Anderson Cancer Center in Houston, Texas.

Tracks 1-15

- Track 1** Perspective on the role of anti-angiogenic therapy in early- and advanced-stage adenocarcinoma of the lung
- Track 2** Erlotinib and bevacizumab as first-line or maintenance therapy for advanced EGFR mutation-positive adenocarcinoma of the lung
- Track 3** Incorporation of ramucirumab with docetaxel as second-line therapy for advanced NSCLC
- Track 4** Therapeutic options for patients with nonsquamous NSCLC
- Track 5** Role of bevacizumab-based therapy in malignant pleural mesothelioma
- Track 6** Results of the Phase III PROCLAIM trial of cisplatin with either pemetrexed or etoposide and thoracic radiation therapy → consolidation chemotherapy for locally advanced nonsquamous NSCLC
- Track 7** **Case discussion:** A 79-year-old man and nonsmoker with metastatic SCC of the lung enters the Phase I KEYNOTE-001 trial and experiences a prolonged partial response with pembrolizumab
- Track 8** Correlation between mutational burden and response to PD-1/PD-L1 blockade in NSCLC
- Track 9** Counseling patients with metastatic SCC of the lung about prognosis and survival probability
- Track 10** Durable response with pembrolizumab on the KEYNOTE-001 trial
- Track 11** Duration of treatment with immune checkpoint inhibitors
- Track 12** **Case discussion:** A 39-year-old man and never smoker with advanced T790M-mutant adenocarcinoma of the lung experiences a durable response with afatinib/cetuximab
- Track 13** Carboplatin/pemetrexed/bevacizumab and pulsed-dose erlotinib in patients with EGFR-mutant central nervous system metastases
- Track 14** Activity of the newly FDA-approved third-generation EGFR tyrosine kinase inhibitor (TKI) osimertinib (AZD9291) in patients with EGFR-mutant advanced NSCLC
- Track 15** Response and tolerability of osimertinib and rociletinib (CO-1686) in advanced T790M-mutant adenocarcinoma of the lung

Select Excerpts from the Interview

Tracks 1-3

- ▶ **DR LOVE:** Do you believe tumor angiogenesis is still a viable research target in advanced NSCLC?
- ▶ **DR HEYMACH:** Several angiogenesis inhibitors prolong OS. Other drugs have prolonged PFS but not OS. It seems that once angiogenesis inhibitors are discontinued, tumors

are able to regrow. This has raised the question of whether to continuously administer angiogenesis inhibitors or to avoid using them in the first place.

Certain mutations appear to be much more responsive to VEGF inhibitors. When erlotinib was tested in combination with bevacizumab without respect to EGFR mutation status in the Phase III BeTa study, it seemed to prolong PFS but no benefit in OS was observed (Herbst 2011). However, in the subgroup of patients with EGFR mutations, a trend appeared in favor of the addition of bevacizumab.

A Phase II study of first-line erlotinib with or without bevacizumab for patients with advanced NSCLC and EGFR mutations demonstrated an impressive benefit with the addition of bevacizumab (Seto 2014). Although they are striking, the findings have not necessarily gained widespread attention. For my patients with lung cancer and EGFR mutations, I like to find a way to administer the combination of bevacizumab and erlotinib. If they are receiving chemotherapy, I often use bevacizumab and erlotinib in the maintenance setting, especially if chemotherapy was initiated before the EGFR status was known.

Sometimes, for my patients with progressive disease on an EGFR inhibitor, I determine if it is feasible to combine bevacizumab with erlotinib, particularly after chemotherapy. I have patients who experience disease progression after receiving erlotinib but end up achieving prolonged stable disease or response with bevacizumab/erlotinib, particularly after chemotherapy. I always try to take advantage of the heightened sensitivity of EGFR-mutant tumors to bevacizumab/erlotinib in one way or the other.

We now have to figure out how to combine anti-angiogenic agents more effectively and determine the subset of patients with the potential to achieve the most benefit.

► **DR LOVE:** What about other anti-angiogenics, particularly the efficacy and tolerability of ramucirumab in squamous versus nonsquamous NSCLC?

► **DR HEYMACH:** The FDA approval for ramucirumab applies to both squamous and nonsquamous cell histologies, unlike bevacizumab, which is used in the nonsquamous setting. In the Phase III REVEL trial, the benefit of ramucirumab/docetaxel was modest. It's not like the benefit that a patient with EGFR-mutant disease yields from an EGFR inhibitor.

However, although it is not enormous, the benefit is real with little additional toxicity. If you're going to administer docetaxel, you have little reason not to add ramucirumab, unless the patient has a serious cardiovascular risk factor, a recent thromboembolic event or a bleeding risk. The regimen is a reasonable option for patients with squamous cell histology, and most of these patients will receive docetaxel, although it will likely be after immunotherapy.

Track 6

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

► **DR HEYMACH:** Two common chemotherapy regimens have been used with radiation therapy in this setting: carboplatin/paclitaxel and cisplatin/etoposide. We usually admin-

ister weekly carboplatin/paclitaxel with radiation therapy. Typically, after completion of chemoradiation therapy, we administer 2 cycles of consolidation carboplatin/paclitaxel once every 3 weeks at full doses. Cisplatin/etoposide is administered on a different schedule with TRT. For this regimen, we often administer docetaxel consolidation after.

Pemetrexed/cisplatin/TRT looks like an intriguing regimen that is arguably better tolerated than etoposide/platinum/TRT in terms of the Grade 3 or 4 hematologic toxicities, but no difference was observed in terms of OS (Senan 2015). We will have to wait to see if other parameters differ between regimens. It'll be interesting to discern whether this regimen begins to be much more widely used in the future.

 **Track 15**

► **DR LOVE:** What is your perspective on the efficacy of the third-generation EGFR tyrosine kinase inhibitors (TKIs) osimertinib and rociletinib in NSCLC?

► **DR HEYMACH:** Both drugs are active specifically in patients with T790M mutations and are well tolerated (2.1, 2.2). Both are highly active in patients with EGFR TKI-refractory disease, with response rates of approximately 60% in the T790M-positive population and 20% in those with T790M mutation-negative disease. I believe both agents will have a role in the T790M-negative patient subgroup.

We now have some preclinical and clinical data documenting resistance to these agents. It involves a new mutation that we will soon be hearing more about, the C797S mutation (Oxnard 2015; Simmons 2015). Presumably, we will need a new generation of drugs able to inhibit both the T790M mutation and C797S-mutated disease.

2.1 Phase I/II AURA Trial: Efficacy and Safety of Osimertinib (AZD9291) for EGFR Mutation-Positive Locally Advanced or Metastatic Non-Small Cell Lung Cancer

Response	Dose-escalation and expansion cohorts		
	All patients (n = 239)	T790M-positive (n = 127)	T790M-negative (n = 61)
ORR	51%	61%	21%
DCR	84%	95%	61%
Survival	n = 222	n = 138	n = 62
Median PFS	8.2 mo	9.6 mo	2.8 mo
Select AEs (Grade ≥3)	20 mg qd (n = 21)	80 mg qd (n = 90)	160 mg qd (n = 63)
Rash	0%	0%	3%
Diarrhea	0%	1%	2%
Nausea	5%	0%	0%
Appetite decrease	5%	1%	0%
Fatigue	5%	0%	0%

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

Jänne PA et al. *N Engl J Med* 2015;372(18):1689-99.

Editor's note: Subsequent to this interview, on November 13, 2015 the FDA granted accelerated approval to osimertinib for the treatment of EGFR T790M mutation-positive advanced NSCLC after disease progression on other EGFR-blocking therapy. ■

2.2

Efficacy and Safety Results from the 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)
Objective response rate	59%	29%
Disease control rate	93%	59%
Median PFS	13.1 mo	5.6 mo
Select AEs (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%

PFS = progression-free survival; AEs = adverse events

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

Press release (November 16, 2015): "In the company's NDA [new drug application] submission, both immature confirmed and unconfirmed response analyses were submitted. As the efficacy data have matured, the number of patients with an unconfirmed response who converted to a confirmed response was lower than expected."

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

SELECT PUBLICATIONS

Herbst RS et al. **Efficacy of bevacizumab plus erlotinib versus erlotinib alone in advanced non-small-cell lung cancer after failure of standard first-line chemotherapy (BeTa): A double-blind, placebo-controlled, phase 3 trial.** *Lancet* 2011;377(9780):1846-54.

Jänne PA et al. **AZD9291 in EGFR inhibitor-resistant non-small-cell lung cancer.** *N Engl J Med* 2015;372(18):1689-99.

Oxnard GR et al. **Mechanisms of acquired resistance to AZD9291 in EGFR T790M positive lung cancer.** *Proc IASLC* 2015;**Abstract ORAL17.07.**

Senan S et al. **Final overall survival (OS) results of the phase III PROCLAIM trial: Pemetrexed (Pem), cisplatin (Cis) or etoposide (Eto), Cis plus thoracic radiation therapy (TRT) followed by consolidation cytotoxic chemotherapy (CTX) in locally advanced nonsquamous non-small cell lung cancer (nsNSCLC).** *Proc ASCO* 2015;**Abstract 7506.**

Sequist LV et al. **Rociletinib in EGFR-mutated non-small-cell lung cancer.** *N Engl J Med* 2015;372(18):1700-9.

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.

Simmons AD et al. **Identification of effective drug combinations to prevent or delay resistance to the EGFR mutant selective inhibitor rociletinib (CO-1686).** *Proc IASLC* 2015;**Abstract 3010/MINI09.04.**



INTERVIEW

Jean-Charles Soria, MD, PhD

Prof Soria is Full Professor at Paris University XI and Head of the Drug Development Department at Institut Gustave Roussy in Villejuif, France.

Tracks 1-15

- Track 1 Case discussion:** A 60-year-old man and former smoker with metastatic SCC of the lung whose disease progresses after 2 cycles of cisplatin/gemcitabine receives second-line nivolumab therapy
- Track 2** Perspective on the use of corticosteroids in patients receiving immune checkpoint inhibitors
- Track 3** Contraindications to the use of immune checkpoint inhibitors
- Track 4** Clinical experience with anti-PD-1 antibody-associated colitis
- Track 5** Evaluation of radiographic scans and monitoring of liver transaminase levels in the determination of “pseudo-progression” versus true disease progression in patients receiving immune checkpoint inhibitors
- Track 6** Third-line therapeutic options for patients with progressive SCC of the lung
- Track 7** Perspective on the use of the VeriStrat® assay for patients with SCC of the lung
- Track 8** Results of the Phase III LUX-Lung 8 trial of second-line afatinib versus erlotinib for patients with advanced SCC of the lung
- Track 9** Use of the VeriStrat assay to evaluate tissue samples from the LUX-Lung 8 study
- Track 10** Selection of EGFR TKI therapy (afatinib versus erlotinib) in patients with pan-wild-type NSCLC
- Track 11** Prophylactic use of anti-diarrheal agents in patients receiving afatinib
- Track 12** Palliative use of laser ablation for patients with stomatitis
- Track 13 Case discussion:** A 75-year-old woman with advanced T790M-mutant adenocarcinoma of the lung receives osimertinib on an expanded access program
- Track 14** Diverse molecular mechanisms of acquired resistance to osimertinib and rociletinib in EGFR-mutant lung cancer
- Track 15** Management of rociletinib-associated hyperglycemia

Select Excerpts from the Interview

Tracks 1, 3

- ▶ **DR LOVE:** Would you discuss your approach to first-line therapy for patients with metastatic SCC of the lung?
- ▶ **PROF SORIA:** Cisplatin/gemcitabine is probably the most popular regimen used in Europe for SCC. Carboplatin/paclitaxel is an alternative, and nanoparticle albumin-bound (*nab*) paclitaxel is an agent that is popular in the United States. It is especially appealing because it does not necessitate the administration of steroids.
- ▶ **DR LOVE:** These days when confronted with a patient with metastatic SCC, many clinicians would likely be thinking about a checkpoint inhibitor at the time of progres-

sion. Do you believe it is advantageous to use an agent prior to that that does not require corticosteroids, such as *nab* paclitaxel?

► **PROF SORIA:** In “real-life” settings, administering corticosteroids before a checkpoint inhibitor won’t change anything. But, of course, when you want to combine an immune checkpoint inhibitor with chemotherapy, being able to use an agent that does not mandate corticosteroids is extremely important. This is one reason why the ongoing Phase III trial evaluating different chemotherapy options, one of which is carboplatin/*nab* paclitaxel, with or without the anti-PD-L1 antibody atezolizumab for chemotherapy-naïve patients with advanced SCC is so intriguing (3.1).

► **DR LOVE:** What are some of the absolute contraindications to using immune checkpoint inhibitors, and do you believe any conditions that are thought to be contraindications actually don’t preclude a patient from receiving these agents?

► **PROF SORIA:** We must realize that the data presented to date regarding the tolerability of immune checkpoint inhibitors are based solely on patients who have been enrolled in clinical trials and, therefore, strict inclusion criteria have been applied to them. Now that these agents are out there in the real world, I don’t believe that most of my colleagues are thoroughly questioning patients as to whether they have a history of autoimmune disorders such as thyroiditis or psoriasis.

I have personal experience from a recent case at our institution when a patient forgot to tell us that he had psoriasis 5 years ago, and it ended up being a nightmare. After the first infusion of nivolumab, he developed extremely severe psoriasis over 50% of the surface of his body that led to him being admitted to the ICU. Extensive psoriasis is a major concern. If it expands, it is not easy to treat. We were unable to continue the immune checkpoint blockade therapy.

Preexisting Crohn’s disease is another contraindication because checkpoint inhibitors can aggravate that condition. With regard to a patient having a history of thyroiditis, I would not consider that to be a contraindication because its treatment is obvious. For hyperthyroiditis, you simply administer beta blockers, and the patient’s thyroid function should decrease. I have heard debate over vitiligo being a contraindication to using these agents, but that is not the case. On the contrary, we’ve seen suggestions

3.1

IMpower 131: A Phase III Trial Evaluating the Efficacy and Safety of the Anti-PD-L1 Antibody Atezolizumab (MPDL3280A) in Combination with Carboplatin/Paclitaxel or with Carboplatin/*Nab* Paclitaxel in Chemotherapy-Naïve Patients with Stage IV Squamous Non-Small Cell Lung Cancer (NSCLC)

Protocol IDs: NCT02367794, G029437

Target Accrual: 1,200 (Open)

Eligibility

- Histologically or cytologically confirmed, treatment-naïve Stage IV squamous NSCLC
- ECOG PS 0-1
- No history of autoimmune disease

R

Atezolizumab + *nab* paclitaxel + carboplatin

Atezolizumab + paclitaxel + carboplatin

Nab paclitaxel + carboplatin

www.clinicaltrials.gov. Accessed January 2016.

that patients who have baseline vitiligo tend to experience better responses to immune checkpoint inhibitors.

On a related note, one piece of advice I like to give to my colleagues who are using immune checkpoint inhibitors is not to underestimate the risk of diarrhea. Also, make sure patients understand that if they experience diarrhea, the worst thing they can do is to start taking loperamide because it will exacerbate the condition.

Tracks 7-9, 11

► **DR LOVE:** What is your view on the utility of the VeriStrat proteomic assay?

► **PROF SORIA:** The data on VeriStrat are interesting. VeriStrat is a blood-based test that aims at providing a score that tells you whether the patient is more likely to benefit from erlotinib versus chemotherapy (Gregorc 2014; [3.2]). To my surprise, the uptake in the use of this assay has been low, at least in Europe. I only know of a few clinicians in Italy who are using this assay in daily practice. I believe that the community has a sense, especially for patients with nonsquamous NSCLC, that EGFR mutation is the true molecular predictor. On the other hand, maybe using this assay for patients with SCC is a reasonable approach.

We are currently using the VeriStrat assay to analyze hundreds of samples from the LUX-Lung 8 trial, and we hope to be able to share the data with the community this year. We previously reported the primary analysis of this trial, which evaluated afatinib versus erlotinib as second-line therapy for patients with advanced SCC after platinum-based chemotherapy.

The advantage was clear in favor of afatinib compared to erlotinib in terms of response rate, disease control rate, PFS and OS, although some might argue that the latter was marginal because it was a 1.1-month advantage. However, it was statistically significant (Soria 2015a; [3.3]). The quality-of-life results convinced me that afatinib was the better alternative.

A lot of people argue that afatinib is a difficult drug to tolerate — that it causes a lot of diarrhea and stomatitis. Although this may be true, the patient-reported outcomes from the study favored afatinib, probably because it provided better tumor control than erlotinib in this setting, so the overall balance is that the patients have a better quality of life with afatinib than with erlotinib.

With regard to afatinib-associated diarrhea, I always prescribe concomitant loperamide. I have quite a bit of experience with afatinib because we have been using it for many

3.2

Phase III PROSE Trial: Predictive Value of the VeriStrat Proteomic Signature in Non-Small Cell Lung Cancer Treated with Second-Line Erlotinib or Chemotherapy

Median overall survival	Erlotinib	Chemotherapy	Hazard ratio	p-value
All patients (n = 134, 129)	7.7 mo	9.0 mo	1.22	0.148
VeriStrat good (n = 96, 88)	11.0 mo	10.9 mo	1.06	0.714
VeriStrat poor (n = 38, 41)	3.0 mo	6.4 mo	1.72	0.022

Gregorc V et al. *Lancet Oncol* 2014;15(7):713-21.

years in various clinical trials, and I never wait for diarrhea to occur. I instruct patients to take 1 loperamide pill a day and then I tell them, “If you experience loose stools, take another.”

We also reported at the recent World Lung Cancer Conference a comprehensive genomic analysis of more than 200 patients on the LUX-Lung 8 trial (Soria 2015b). That analysis was unable to identify any subgroup of patients who experienced a greater advantage compared to the overall patient population. Afatinib was better than erlotinib in all of the molecular subgroups that we analyzed. We demonstrated that EGFR mutations do not explain why afatinib is better in this setting. ■

3.3

LUX-Lung 8: Results of a Phase III Trial of Afatinib versus Erlotinib as Second-Line Therapy for Patients with Advanced Squamous Cell Carcinoma of the Lung

Efficacy	Afatinib (n = 398)	Erlotinib (n = 397)	Hazard ratio	p-value
Median progression-free survival	2.6 mo	1.9 mo	0.81	0.0103
Median overall survival	7.9 mo	6.8 mo	0.81	0.0077
Disease control rate	51%	40%	—	0.0020
Objective response rate	6%	3%	—	0.0551
	Afatinib (n = 392)		Erlotinib (n = 395)	
Select adverse events	Grade 1/2	Grade 3/4	Grade 1/2	Grade 3/4*
Diarrhea	59.4%	10.5%	30.9%	2.5%
Rash or acne	61.2%	5.9%	57.0%	10.4%
Stomatitis	24.7%	4.1%	8.6%	0%
Fatigue	13.5%	1.5%	10.4%	1.8%
Nausea	12.2%	1.0%	6.3%	0.8%
Decreased appetite	12.0%	0.8%	9.9%	0.5%
Paronychia	9.9%	0.5%	4.1%	0.3%

* Incidence of Grade 4 diarrhea with afatinib (n = 2) and erlotinib (n = 1); Grade 4 dehydration with afatinib (n = 4) and erlotinib (n = 0)

Soria JC et al; LUX-Lung 8 Investigators. *Lancet Oncol* 2015a;16(8):897-907.

SELECT PUBLICATIONS

Gregorc V et al. **Predictive value of a proteomic signature in patients with non-small-cell lung cancer treated with second-line erlotinib or chemotherapy (PROSE): A biomarker-stratified, randomised phase 3 trial.** *Lancet Oncol* 2014;15(7):713-21.

Kuiper JL et al. **VeriStrat® has prognostic value in advanced stage NSCLC patients treated with erlotinib and sorafenib.** *Br J Cancer* 2012;107(11):1820-5.

Soria JC et al; LUX-Lung 8 Investigators. **Afatinib versus erlotinib as second-line treatment of patients with advanced squamous cell carcinoma of the lung (LUX-Lung 8): An open-label randomized controlled phase 3 trial.** *Lancet Oncol* 2015a;16(8):897-907.

Soria JC et al. **Tumor genomic analysis from LUX-Lung 8: A Phase III trial of afatinib versus erlotinib in squamous cell carcinoma of the lung.** *Proc IASLC* 2015b; **Abstract ORAL32.01.**

Stinchcombe TE et al. **A retrospective analysis of VeriStrat status on outcome of a randomized phase II trial of first-line therapy with gemcitabine, erlotinib, or the combination in elderly patients (age 70 years or older) with stage IIIB/IV non-small-cell lung cancer.** *J Thorac Oncol* 2013;8(4):443-51.



INTERVIEW

Martin Reck, MD, PhD

Dr Reck is Head of the Department of Thoracic Oncology and the Clinical Trial Department at LungenClinic Grosshansdorf in Grosshansdorf, Germany.

Tracks 1-5

- Track 1** Activity and tolerability of the newly FDA-approved anti-EGFR antibody necitumumab in advanced SCC of the lung
- Track 2** **Case discussion:** A 68-year-old man and smoker with locally advanced SCC of the lung treated with cisplatin/vinorelbine and radiation therapy
- Track 3** Therapeutic options for second-line therapy of Stage III SCC of the lung
- Track 4** **Case discussion:** A 70-year-old man and smoker with Stage IV SCC of the lung and comorbidities who receives carboplatin-based chemotherapy
- Track 5** Counseling patients with progressive SCC of the lung about immune checkpoint inhibitors and other treatment options

Select Excerpts from the Interview

Track 1

- ▶ **DR LOVE:** Would you discuss the efficacy of the recently FDA-approved anti-EGFR antibody necitumumab in combination with chemotherapy for advanced SCC?
- ▶ **DR RECK:** Necitumumab is a human monoclonal antibody directed against EGFR, and it has been investigated in combination with cisplatin/gemcitabine and compared to cisplatin/gemcitabine alone as first-line therapy in the large, randomized Phase III SQUIRE trial for patients with advanced SCC (Thatcher 2015; [4.1]). The trial was positive. The primary endpoint was OS, and we observed a significant improvement favoring the combination of cisplatin/gemcitabine and necitumumab. We also observed an improvement in PFS, although it was marginal. An important question is whether these findings are clinically relevant.
- ▶ **DR LOVE:** Do you believe the necitumumab/gemcitabine/cisplatin combination is worth using?
- ▶ **DR RECK:** Yes. I believe that currently we have limited treatment options in the first-line setting for patients with SCC, so everything that contributes to an improvement in outcome for the patient is welcome. I would use it, but we must recognize the tolerability and the cost. All of this of course plays a role in the selection of treatment.
- ▶ **DR LOVE:** What kinds of side effects have you observed clinically with necitumumab treatment? Is it similar to cetuximab in that regard?

SQUIRE: Results of a Phase III Trial of First-Line Gemcitabine/Cisplatin (Gem/Cis) with or without Necitumumab for Stage IV Squamous Cell Non-Small Cell Lung Cancer

	Gem/cis + necitumumab (n = 545)	Gem/cis (n = 548)	Hazard ratio	p-value
Median OS	11.5 mo	9.9 mo	0.84	0.01
Median PFS	5.7 mo	5.5 mo	0.85	0.020
ORR	31%	29%	—	0.400
Select Grade ≥3 AEs	Gem/cis + necitumumab (n = 538)		Gem/cis (n = 541)	
Neutropenia	24.0%		27.5%	
Anemia	10.6%		10.9%	
Thrombocytopenia	10.0%		10.0%	
Fatigue	7.2%		7.0%	
Hypomagnesemia	9.0%		1.0%	
Skin rash	7.0%		0.4%	
Venous thromboembolic events	5.0%		2.6%	

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

Thatcher N et al. *Lancet Oncol* 2015;16(7):763-74.

► **DR RECK:** The most significant side effects observed in the Phase III FLEX trial of cetuximab were rash, infusion reaction and an increase in myelotoxicity (Pirker 2009). In the SQUIRE trial, again rash was a predominant adverse event associated with necitumumab (Thatcher 2015; [4.1]). Patients who receive necitumumab avoid some of the side effects associated with cetuximab.

Tracks 4-5

► **CASE DISCUSSION:** A 70-year-old man and smoker with Stage IV SCC

► **DR RECK:** I believe this case is representative of the everyday patient with SCC whom you see in the clinic. The patient was in poor condition and certainly not a candidate for cisplatin-based chemotherapy, so we offered carboplatin/gemcitabine. We added bisphosphonates given that the patient also had bone metastases, and the course went well, more or less, with stable disease and a minor response. The treatment was tolerable for the most part, although he did develop some fatigue and myelotoxicity. He also experienced some thrombocytopenia, so we had to modify the gemcitabine dose.

This is something we see frequently with this kind of disease. I take into account the general performance status of the patient, and if the patient is frail, I'm extremely cautious when considering platinum-based chemotherapy. You must be realistic, weighing potential tolerability issues against the response rates in SCC and the efficacy you may observe with platinum-based chemotherapy.

► **DR LOVE:** How do you counsel a patient like this who develops disease progression? What about an immune checkpoint inhibitor?

► **DR RECK:** This patient experienced a PFS of 3 months, which we see frequently in SCC. At that time nivolumab was not available, so he received 4 cycles of second-line docetaxel, but we could achieve only tumor stabilization.

A checkpoint inhibitor would probably be the next option to discuss with him. Is he a candidate for nivolumab? We must be realistic. The prognosis for patients with squamous cell lung cancer is inferior to that for patients with nonsquamous disease, but we do see improvements, and it's important to consider the opportunities because 30% of our patients present with advanced SCC.

We have put a lot of effort into targeted therapies for SCC, and trials are still ongoing (4.2). We have studied PI3K inhibitors in patients with PI3K alterations and FGF inhibitors in patients with FGF amplification. Overall, signs of limited efficacy have emerged, but I'm not sure whether this will be a breakthrough for patients with SCC like the EGFR TKIs have been in EGFR-mutated tumors. ■

4.2 Select Ongoing Trials for Patients with Metastatic Squamous Cell Carcinoma of the Lung

Targeted therapies				
Trial identifiers	Phase	N	Disease setting	Treatment arms
SWOG-S1400 (NCT02154490)	II/III	10,000	<ul style="list-style-type: none"> Recurrent disease Stage IIIB-IV 	<ul style="list-style-type: none"> Durvalumab (MEDI4736) Docetaxel Taselisib (GDC-0032) Palbociclib AZD4547 Rilotumumab/erlotinib Erlotinib
CEDAR (NCT02423590)	II	140	<ul style="list-style-type: none"> Advanced disease 	<ul style="list-style-type: none"> Gemcitabine/carboplatin/apatorsen (OGX-427) Gemcitabine/carboplatin
NCT02428764	II	37	<ul style="list-style-type: none"> Unresectable disease Stage III 	<ul style="list-style-type: none"> Nimotuzumab/gemcitabine/carboplatin → surgery
Immune checkpoint inhibitors				
Trial identifiers	Phase	N	Disease setting	Treatment arms
IMpower 111 (NCT02409355)	III	400	<ul style="list-style-type: none"> Chemotherapy-naïve disease Stage IV 	<ul style="list-style-type: none"> Atezolizumab (MPDL3280A) Gemcitabine + carboplatin or cisplatin
IMpower 131 (NCT02367794)	III	1,200	<ul style="list-style-type: none"> Chemotherapy-naïve disease Stage IV 	<ul style="list-style-type: none"> Atezolizumab/<i>nab</i> paclitaxel/carboplatin Atezolizumab/paclitaxel/carboplatin <i>Nab</i> paclitaxel/carboplatin

www.clinicaltrials.gov. Accessed January 2016.

SELECT PUBLICATIONS

Pirker R et al. **Cetuximab plus chemotherapy in patients with advanced non-small-cell lung cancer (FLEX): An open-label randomised phase III trial.** *Lancet* 2009;373(9674):1525-31.

Thatcher N et al. **Necitumumab plus gemcitabine and cisplatin versus gemcitabine and cisplatin alone as first-line therapy in patients with stage IV squamous non-small-cell lung cancer (SQUIRE): An open-label, randomised, controlled phase 3 trial.** *Lancet Oncol* 2015;16(7):763-74.

QUESTIONS (PLEASE CIRCLE ANSWER):

1. In a study evaluating the clinical utility of NGS, genomic alterations were uncovered using NGS in tumors from _____ of patients who were previously found to have “pan-negative” disease by non-NGS methods.
 - a. 35%
 - b. 75%
 - c. 94%
2. A Phase II trial of cabozantinib for patients with advanced RET-rearranged NSCLC demonstrated which of the following side effects?
 - a. Elevated transaminases
 - b. Diarrhea
 - c. Skin/hair hypopigmentation
 - d. All of the above
3. A Phase II study evaluating the BRAF inhibitor dabrafenib in combination with the MEK inhibitor trametinib demonstrated the combination to be efficacious for patients with BRAF V600E mutation-positive metastatic NSCLC.
 - a. True
 - b. False
4. The results of the Phase III PROCLAIM trial for previously untreated locally advanced nonsquamous NSCLC demonstrated a statistically significant improvement in OS with pemetrexed/cisplatin and TRT versus etoposide/cisplatin/TRT followed by consolidation chemotherapy.
 - a. True
 - b. False
5. 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 third-generation EGFR inhibitors demonstrated greater efficacy among the population of patients with _____.
 - a. EGFR T790M mutation-positive disease
 - b. EGFR T790M mutation-negative disease
6. The Phase III IMpower 131 trial is evaluating the addition of the anti-PD-L1 antibody atezolizumab to _____ for patients with chemotherapy-naïve Stage IV squamous cell NSCLC.
 - a. Paclitaxel/carboplatin
 - b. Nab paclitaxel/carboplatin
 - c. Docetaxel/carboplatin
 - d. Both a and b
 - e. Both b and c
7. The results of the Phase III PROSE trial for patients with inoperable NSCLC demonstrated that those with disease classified as VeriStrat poor had a better survival outcome with chemotherapy than with erlotinib in the second-line setting.
 - a. True
 - b. False
8. The Phase III LUX-Lung 8 trial demonstrated statistically significant improvements in _____ with afatinib versus erlotinib as second-line therapy for patients with advanced squamous cell NSCLC.
 - a. PFS
 - b. OS
 - c. Both a and b
 - d. Neither a nor b
9. The Phase III SQUIRE trial demonstrated a statistically significant OS benefit with the addition of necitumumab to gemcitabine/cisplatin as first-line therapy for patients with Stage IV squamous cell NSCLC.
 - a. True
 - b. False
10. The FDA approval of ramucirumab for metastatic NSCLC after disease progression on platinum-based chemotherapy is for patients with _____ histology.
 - a. Squamous
 - b. Nonsquamous
 - c. Both a and b

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
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
Activity and safety of new agents (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
Erlotinib and bevacizumab as first-line therapy for advanced EGFR mutation-positive nonsquamous NSCLC	4 3 2 1	4 3 2 1
Activity and tolerability of the newly FDA-approved anti-EGFR antibody necitumumab in advanced SCC of the lung	4 3 2 1	4 3 2 1
Results of the Phase III LUX-Lung 8 trial of second-line afatinib versus erlotinib for patients with advanced SCC	4 3 2 1	4 3 2 1
Available data with BRAF/MEK inhibitor combinations in patients with BRAF V600E-mutant disease	4 3 2 1	4 3 2 1
IMpower 131: A Phase III study of the anti-PD-L1 antibody atezolizumab (MPDL3280A) in combination with carboplatin/paclitaxel or with carboplatin/ <i>nab</i> paclitaxel in chemotherapy-naïve Stage IV SCC	4 3 2 1	4 3 2 1
Autoimmune contraindications to immune checkpoint inhibition	4 3 2 1	4 3 2 1
Clinical significance of RET rearrangements and implications for the selection of chemotherapy and targeted therapy	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:

- Recall the scientific rationale for ongoing investigation of novel agents or immunotherapeutic approaches in lung cancer, and counsel appropriately selected patients about study participation. 4 3 2 1 N/M N/A
- Assess available research evidence with existing and emerging therapeutic options for patients with advanced squamous cell carcinoma of the lung, and use this information to guide clinical care and protocol opportunities for these individuals. 4 3 2 1 N/M N/A
- Employ an understanding of next-generation sequencing, and determine its clinical and/or research application for patients with metastatic lung cancer. 4 3 2 1 N/M N/A

EDUCATIONAL ASSESSMENT AND CREDIT FORM (continued)

- 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 use this information to develop optimal therapeutic approaches 4 3 2 1 N/M N/A
- Formulate a plan to incorporate checkpoint inhibitor therapy into the treatment of advanced non-small cell lung cancer and subsequently monitor immune-related side effects when they occur 4 3 2 1 N/M N/A

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

Would you recommend this activity to a colleague?

Yes No If no, please explain:

Additional comments about this activity:

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

		4 = Excellent				3 = Good				2 = Adequate				1 = Suboptimal			
Faculty		Knowledge of subject matter				Effectiveness as an educator											
Alexander E Drilon, MD		4	3	2	1	4	3	2	1								
John V Heymach, MD, PhD		4	3	2	1	4	3	2	1								
Jean-Charles Soria, MD, PhD		4	3	2	1	4	3	2	1								
Martin Reck, 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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