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Lung Cancer™ UPDATE

Conversations with Oncology Investigators

Bridging the Gap between Research and Patient Care

FACULTY INTERVIEWS

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EDITOR

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2 Audio CDs
Monograph

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Lung Cancer Update
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OVERVIEW OF ACTIVITY

Lung cancer is the leading cause of cancer mortality in the United States for both men and women, resulting in more deaths than breast, prostate, colon and pancreatic cancer combined. Progress in the screening, prevention and treatment of this disease has been limited, and approximately 85% of patients who develop lung cancer will die of it. Traditional chemotherapy, surgery and radiation therapy have had a modest effect on long-term outcomes. However, the advent of biologic 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

- 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 mutations.
- Recall the scientific rationale for the ongoing investigation of novel agents or immunotherapeutic approaches in lung cancer, and counsel appropriately selected patients about study participation.
- Employ an understanding of next-generation sequencing, 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 investigational therapeutic opportunities to circumvent this process.
- Develop an evidence-based approach to the selection of induction and maintenance biologic therapy and/or chemotherapy for patients with advanced non-small cell lung cancer.
- Consider the use of multimodality therapy for appropriate patients with mesothelioma who may potentially be cured with this approach.

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INTERVIEW

D Ross Camidge, MD, PhD

Dr Camidge is Director of the Thoracic Oncology Clinical Program and Associate Director for Clinical Research at the University of Colorado Cancer Center in Aurora, Colorado.

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Track 3 Management of treatment-associated hyperglycemia with the third-generation, irreversible EGFR TKI rociletinib (CO-1686)

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Select Excerpts from the Interview

Track 2

DR LOVE: What is your approach to patients with EGFR-mutant non-small cell lung cancer (NSCLC) who develop acquired resistance to an EGFR tyrosine kinase inhibitor (TKI) such as erlotinib?

DR CAMIDGE: There is currently a debate as to whether patients with EGFR-mutant lung cancer who develop resistance to erlotinib should be taken off erlotinib. No one

has proven whether the re-treatment approach is better or worse than continuing TKI therapy and adding in chemotherapy. Patients who develop acquired resistance to TKIs respond well to chemotherapy. When they receive re-treatment with the TKI, they may have a good response. I believe that we should aim to suppress as many cancerous clones as possible. I have changed my approach in recent years. I continue to administer erlotinib to patients who develop disease progression while receiving the drug, and I add in chemotherapy.

The mechanisms of acquired resistance in cancer cells change, depending on the environment they're adapting to. The T790M resistance mutation in the EGFR tyrosine kinase cripples the kinase, resulting in a relatively indolent clone that does not survive well in the absence of erlotinib. Patients who have been off erlotinib for some time will rerespond well to erlotinib, though the duration of response is shorter.

Editor's note: Subsequent to this interview, data were presented by Dr Tony Mok and colleagues at ESMO 2014 on the Phase III IMPRESS trial evaluating gefitinib/chemotherapy versus chemotherapy for EGFR mutation-positive NSCLC after disease progression on first-line gefitinib. The authors concluded that continuation of gefitinib in addition to cisplatin/pemetrexed would be of no clinical benefit for patients with acquired resistance to gefitinib (Mok T et al. *Proc ESMO* 2014;**Abstract LBA2_PR**).

Tracks 3-4

DR LOVE: What do we know about the efficacy of the third-generation EGFR TKIs HM61713, AZD9291 and rociletinib (CO-1686) for EGFR TKI-resistant NSCLC?

DR CAMIDGE: Third-generation EGFR TKIs are designed to have activity against common EGFR activating mutations and the T790M mutation while sparing wild-type EGFR. HM61713 elicits a disappointingly low response rate of approximately 20% in patients who develop disease progression on EGFR TKIs (Kim 2014a).

I believe it's turning into a "2-horse race" between rociletinib and AZD9291, both of which have good activity. In patients who have the T790M mutation, AZD9291 demonstrated a 64% response rate. In the T790M-negative cohort, the response rate was 22% (Janne 2014). With rociletinib the response rate was 58% (Sequist 2014).

Rociletinib and AZD9291 have yielded impressive progression-free survival (PFS) curves. Although the data are not mature, the median PFS for rociletinib is more than 12 months. We have to await further data to determine if one is superior.

DR LOVE: What side effects are observed with rociletinib and AZD9291?

DR CAMIDGE: Hyperglycemia is a relatively common side effect of rociletinib. This is drug-induced diabetes, and it doesn't happen in all patients. In a study presented at the ASCO 2014 meeting, hyperglycemia and impaired glucose tolerance were reported in more than 50% of patients, with Grade 3 hyperglycemia occurring in approximately 20% of patients (Sequist 2014; [1.1]). Hyperglycemia can be managed with oral antihyperglycemic drugs, but some patients may require insulin.

Hyperglycemia doesn't appear to be a problem with AZD9291. Some patients experience rash. Grade 3 or higher adverse events were observed in approximately 20% of

patients at the 80-mg dose of AZD9291, which is the dose being used moving forward (Janne 2014; [1.1]).

1.1

Efficacy and Safety of Third-Generation EGFR Inhibitors AZD9291 and Rociletinib for EGFR-Resistant NSCLC

Efficacy	AZD9291*[1] (n = 61)	Rociletinib[2] (n = 40)
Overall response rate	54%	58%
Select adverse events (any grade)	**AZD9291*** **(n = 74)**	**Rociletinib** **(n = 72)**
Diarrhea	20%	23.6%
Rash	27%	4%
Nausea	14%	34.7%
Hyperglycemia	1%	52.7%†
QT prolongation	1%	15.3%

* At Phase II dose of 80 mg; † Including impaired glucose tolerance

[1] Janne P et al. *Proc ASCO* 2014;**Abstract 8009**; [2] Sequist L et al. *Proc ASCO* 2014;**Abstract 8010**.

Track 5

DR LOVE: Would you discuss the recent paper that you were part of that investigated the combination afatinib/cetuximab in patients with EGFR-mutant NSCLC with acquired resistance to EGFR TKIs (Janjigian 2014)?

DR CAMIDGE: Afatinib/cetuximab is an interesting combination that shuts off all EGFR signaling. In our study, 126 patients with EGFR-mutant NSCLC received the combination of afatinib and cetuximab. The overall response rate was 32% in patients harboring T790M-positive tumors and 25% in the T790M-negative cohort, with a duration of response of 5.7 months. The median PFS was 4.7 months (Janjigian 2014; [1.2]).

The side effects of the combination were significant. Approximately 40% of patients needed a dose reduction, mostly because of skin toxicity and diarrhea. The afatinib/cetuximab combination is being investigated by SWOG as an alternative to afatinib as first-line therapy. Though the combination is relatively toxic, it can offer a few additional months of disease control.

DR LOVE: Would you discuss your recent review titled "Acquired resistance to TKIs in solid tumors: Learning from lung cancer" (Camidge 2014a)?

DR CAMIDGE: The review discussed some of the approaches that can be used after the development of acquired resistance to TKI therapy. We discussed different options, including stopping the TKI and switching to chemotherapy, staying on the TKI and adding in chemotherapy or switching to a new agent, such as an immune checkpoint inhibitor. The emerging and still controversial role of focused radiation therapy for isolated areas of disease progression was also discussed. All of these strategies were presented so that you have a menu card of options that could be considered.

1.2

Phase Ib Trial of Afatinib/Cetuximab for Patients with EGFR-Mutant Non-Small Cell Lung Cancer and Acquired Resistance to Erlotinib or Gefitinib

Clinical outcome	T790M mutation status: T790M+ (n = 71)	T790M mutation status: T790M- (n = 53)	Total (n = 126)
Confirmed OR	32%	25%	29%
Median DoR	5.6 mo	9.5 mo	5.7 mo
Median PFS	4.8 mo	4.6 mo	4.7 mo
Adverse events (n = 126)	**All grades**		**Grade 3/4**
Rash	90%		20%
Diarrhea	71%		6%
Fatigue	47%		3%
Nausea	42%		2%
Xerosis	42%		2%
Stomatitis	56%		1%

OR = overall response; DoR = duration of response; PFS = progression-free survival

No significant difference in OR rate ($p = 0.341$) or PFS ($p = 0.643$) between patients with T790M-positive and T790M-negative tumors

Janjigian YY et al. *Cancer Discovery* 2014;4(9):1036–45.

Tracks 9-10, 13-14

DR LOVE: Moving on to patients with ALK gene rearrangements, what is known about the response to the recently approved TKI ceritinib in patients with ALK-rearranged NSCLC and brain metastases?

DR CAMIDGE: At ASCO 2014, Dr Kim presented the best available data from the Phase I ASCEND-1 trial on the activity of ceritinib at the 750-mg dose in patients who previously received ALK inhibitors and had brain metastases, but the sample size was only 10. In this relatively small data set a response rate of 40% was observed (Kim 2014b; [1.3]).

Ceritinib is not well tolerated at 750 mg. Approximately 60% of patients required a dose reduction. I had a patient who responded well to the 750-mg dose of ceritinib, but he found it difficult to tolerate because of gastrointestinal toxicities. The dose was reduced to 600 mg, which he tolerated much better. However, after 10 months of therapy he developed extensive brain metastases.

When you reduce the dose of an agent, it may still be effective systemically, but the exposure in the brain may be dramatically lower. The brain is emerging as the battleground that we have to watch out for even with the second-generation drugs.

DR LOVE: What is known about the efficacy of crizotinib in patients who have ALK-rearranged disease and brain metastases?

DR CAMIDGE: Retrospective data show that crizotinib has activity in the brain, but the intracranial response rate is much lower than that reported systemically. The duration of those responses is at least half that in the body. So it's not entering the brain in most patients.

DR LOVE: What is your approach to caring for patients with ALK-positive NSCLC who are receiving crizotinib and develop extra-CNS oligoprogressive disease?

DR CAMIDGE: Our data show that stereotactic radiation therapy can durably control sites of extra-CNS disease in patients with ALK-positive disease receiving crizotinib. A single course of local ablative therapy was associated with 4 months of PFS benefit. With longer follow-up, the median PFS extension with local ablative therapy was 5.5 months (Gan 2014).

DR LOVE: Besides ceritinib, what are the other promising second-generation ALK inhibitors?

DR CAMIDGE: Alectinib is another second-generation ALK inhibitor that is promising. A Phase II study investigating alectinib in patients with crizotinib-resistant ALK-positive NSCLC is nearing completion (NCT01801111). If that shows that alectinib is effective, it could lead to compassionate access for this agent relatively soon. ALEX is an ongoing Phase III study comparing alectinib to crizotinib in treatment-naïve, ALK-positive advanced NSCLC (NCT02075840). ■

1.3

Phase I ASCEND-1: Ceritinib in Advanced ALK-Rearranged Non-Small Cell Lung Cancer

Efficacy	ALK inhibitor treated	ALK inhibitor naïve	Overall
All patients (n = 163, 83, 246)			
Overall response rate	54.6%	66.3%	58.5%
Complete response	1.2%	1.2%	1.2%
Partial response	53.4%	65.1%	57.3%
Overall intracranial response rate in patients with brain metastases at baseline (n = 10, 4, 14)	40.0%	75.0%	50.0%

Select adverse events (n = 255)	Any grade	Grade 3/4
Diarrhea	86%	6%
Nausea	80%	4%
Vomiting	60%	4%
Fatigue	52%	5%
Elevated ALT	80%	27%
Elevated AST	75%	13%

Kim D et al. *Proc ASCO* 2014b;**Abstract 8003**.

SELECT PUBLICATIONS

Camidge RD et al. **Acquired resistance to TKIs in solid tumours: Learning from lung cancer.** *Nat Rev Clin Oncol* 2014a;11(8):473-81.

Camidge RD et al. **Efficacy and safety of crizotinib in patients with advanced c-MET-amplified non-small cell lung cancer (NSCLC).** *Proc ASCO* 2014b;**Abstract 8001**.

Gan GN et al. **Stereotactic radiation therapy can safely and durably control sites of extra-central nervous system oligoprogressive disease in anaplastic lymphoma kinase-positive lung cancer patients receiving crizotinib.** *Int J Radiat Oncol Biol Phys* 2014;88(4):892-8.

Kim DW et al. **Clinical activity and safety of HM61713, an EGFR-mutant selective inhibitor, in advanced non-small cell lung cancer (NSCLC) patients (pts) with EGFR mutations who had received EGFR tyrosine kinase inhibitors (TKIs).** *Proc ASCO* 2014a;**Abstract 8011**.

INTERVIEW

Corey J Langer, MD

Dr Langer is Director of Thoracic Oncology at the Abramson Cancer Center, Professor of Medicine at Perelman School of Medicine and Vice Chair of the Radiation Therapy Oncology Group at the University of Pennsylvania in Philadelphia, Pennsylvania.

Tracks 1-14

Track 1 **Case discussion:** A 76-year-old man who previously received multiple lines of local and systemic therapy for a multifocal SCC of the lung experiences an excellent response to the anti-PD-1 antibody pembrolizumab (MK-3475) on a clinical trial

Track 2 Clinical experience with and dosing of nanoparticle albumin-bound (*nab*) paclitaxel for patients with SCC and elderly patients with NSCLC

Track 3 Clinical activity and tolerability of pembrolizumab in PD-L1-negative SCC

Track 4 Ongoing and future trial strategies evaluating immune checkpoint inhibitors in NSCLC

Track 5 Common side effects of anti-PD-1 and anti-PD-L1 antibodies

Track 6 Chimeric antigen receptor-directed therapy in thoracic tumors

Track 7 **Case discussion:** An 89-year-old former heavy smoker with Stage IIIA, poorly differentiated SCC of the lung

Track 8 RTOG-1306/Alliance 31101: An ongoing randomized Phase II study of erlotinib or crizotinib prior to chemoradiation therapy for Stage III NSCLC

Track 9 **Case discussion:** A 65-year-old never smoker who underwent treatment 9 years ago for metastatic adenocarcinoma presents with progressive disease and is now found to harbor an ALK rearrangement

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Track 11 Joint analysis of elderly patients on the Phase III PointBreak and ECOG-E4599 trials: Paclitaxel/carboplatin with bevacizumab as first-line therapy for nonsquamous NSCLC

Track 12 Activity of pemetrexed as second-line therapy for patients with ALK-positive NSCLC

Track 13 Perspective on the use of the VeriStrat® assay in clinical practice

Track 14 Recently approved and novel second- and third-generation ALK inhibitors

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DR LOVE: What is your approach to first-line and to maintenance therapy for patients with pan-wild-type adenocarcinoma of the lung?

DR LANGER: I will typically initially administer pemetrexed/carboplatin to these patients, and I will frequently graft bevacizumab onto that regimen if the patient has no contraindications (eg, active brain metastases, antecedent hemoptysis or ongoing thromboembolic phenomena).

Some may argue against such an approach by citing the PointBreak trial results, which compared pemetrexed/carboplatin/bevacizumab to paclitaxel/carboplatin/bevacizumab and reported no obvious survival advantage (Patel 2013). I believe from a toxicity standpoint, pemetrexed/carboplatin/bevacizumab is far better tolerated. Patients develop less neuropathy and alopecia, so their sense of wellbeing is much less impaired. And remember, they're only undergoing treatment every 3 weeks.

If the patient's condition has stabilized or a response is evident after 4 to 6 cycles, I continue pemetrexed and bevacizumab as maintenance therapy if possible. I do not have overall survival (OS) data to justify that approach, but we do have PFS data from the AVAPERL trial comparing bevacizumab to pemetrexed/bevacizumab as maintenance therapy. The authors reported a 3.7-month improvement in PFS with the combination. A trend toward improved survival was also apparent, but the trial was underpowered to demonstrate a survival benefit (Barlesi 2014).

A landmark analysis of the maintenance portion of the PointBreak trial reported about a 2-month difference in OS and PFS between the pemetrexed/bevacizumab combination and the control arm of bevacizumab. Unfortunately we have not seen the *p*-values or the hazard ratios for that analysis.

If a patient is older or has compromised renal function, I will frequently administer taxanes, either weekly paclitaxel or weekly *nab* paclitaxel. Remember, pemetrexed is not reliable or necessarily safe if the creatinine clearance is below 45. There's a relative paucity of data in that situation and highly unpredictable pharmacokinetics.

DR LOVE: Do you currently use *nab* paclitaxel in any other situations, and what is your clinical experience with its dosing in NSCLC?

DR LANGER: I administer *nab* paclitaxel to patients who are aged 70 or older and to patients with squamous cell NSCLC. I generally dose it weekly in order to reduce the peripheral neuropathy that is typically observed with solvent-based paclitaxel administered every 3 weeks. In preference to an uninterrupted schedule, I administer 80 to 100 mg/m^2 weekly for 3 weeks in a row and then allow a week off. I combine the *nab* paclitaxel with carboplatin, which is dosed at AUC 6 every 4 weeks. I find this to be an extraordinarily well-tolerated regimen. Even though many of these patients experience some neuropathy, it's generally quite mild and usually reverses a little faster and more profoundly than with solvent-based paclitaxel.

Track 11

DR LOVE: Any thoughts about the recent data evaluting bevacizumab in older patients?

DR LANGER: A secondary retrospective analysis of ECOG-E4599 by Suresh Ramalingam and colleagues evaluating bevacizumab in combination with chemotherapy versus chemotherapy alone for patients older than age 70 reported a trend toward superior PFS with the combination but no obvious OS advantage. As one might expect, a lot more toxicity occurred with the combination (Ramalingam 2008).

We performed a joint analysis of the PointBreak and ECOG-E4599 trials, comparing the paclitaxel/carboplatin/bevacizumab arms of both to the control arm from E4599 of paclitaxel/carboplatin alone. Obviously caveats apply to such an analysis, but these 2 trials had virtually identical eligibility criteria, and although they weren't contemporaneous,

they weren't so many years apart as to produce major differences in outcome. In this joint analysis the hazard ratio for the survival advantage with bevacizumab persists up until the age of 75. Beyond 75, that advantage is lost (Langer 2013; [2.1]). If anything, the control group fared a little better and the heightened toxicity continued. But nevertheless, on the basis of these data, which are virtually the only data that exist for patients between 70 and 75, I'll still offer bevacizumab. I'm a lot less enthused for patients beyond age 75.

2.1

Joint Analysis of the PointBreak and ECOG-E4599 Trial Results by Patient Age: Hazard Ratios for Paclitaxel/Carboplatin/Bevacizumab versus Paclitaxel/Carboplatin as First-Line Therapy for Nonsquamous Non-Small Cell Lung Cancer

	<65 years (n = 735)	65-75 years (n = 453)	70-75 years (n = 203)	<75 years (n = 1,188)	≥75 years (n = 157)
Overall survival	0.75 $p < 0.01$	0.80 $p = 0.05$	0.68 $p = 0.03$	0.78 $p < 0.01$	1.05 $p = 0.83$
Progression-free survival	0.71 $p < 0.01$	0.62 $p < 0.01$	0.57 $p < 0.01$	0.69 $p < 0.01$	0.95 $p = 0.80$

Langer CL et al. *Proc ASCO* 2013;Abstract 8073.

Tracks 3-4

DR LOVE: What are some of the ongoing and future approaches for using immune checkpoint inhibitors in the treatment of NSCLC?

DR LANGER: A significant proportion of patients with heavily pretreated advanced NSCLC seem to derive benefit from this class of compounds. Responses often continue for well over a year on observation without maintenance treatment (Brahmer 2012). That flies in the face of our typical approach with maintenance therapy.

Studies are now investigating this class of agents up front. The multiarm Phase I CheckMate 012 trial is investigating the anti-PD-1 antibody nivolumab in combination with platinum-based doublets, bevacizumab maintenance, erlotinib and ipilimumab or as monotherapy for newly diagnosed and Stage IIIB/IV NSCLC. Tremendous interest exists in combining anti-PD-1 agents with other immunotherapies, such as CTLA-4 inhibitors (NCT01928394). However, this combination may cause more toxicity than patients with advanced NSCLC can handle because they are generally older with more comorbidities than patients with melanoma. ■

SELECT PUBLICATIONS

Barlesi F et al. **Maintenance bevacizumab-pemetrexed after first-line cisplatin-pemetrexed-bevacizumab for advanced nonsquamous nonsmall-cell lung cancer: Updated survival analysis of the AVAPERL (MO22089) randomized phase III trial.** *Ann Oncol* 2014;25(5):1044-52.

Brahmer JR et al. **Safety and activity of anti-PD-L1 antibody in patients with advanced cancer.** *N Engl J Med* 2012;366(26):2455-65.

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.

Ramalingam SS et al. **Outcomes for elderly, advanced-stage non small-cell lung cancer patients treated with bevacizumab in combination with carboplatin and paclitaxel: Analysis of Eastern Cooperative Oncology Group Trial 4599.** *J Clin Oncol* 2008;26(1):60-5.

INTERVIEW

Anne S Tsao, MD

Dr Tsao is Associate Professor and Director of the Mesothelioma Program in The University of Texas MD Anderson Cancer Center's Department of Thoracic/Head and Neck Medical Oncology in Houston, Texas.

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Track 2	Efficacy of and quality of life after video-assisted thoracoscopic partial pleurectomy versus talc pleurodesis in patients with malignant pleural mesothelioma
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Track 10	Efficacy and toxicity profiles of crizotinib versus second- and third-generation ALK inhibitors

Select Excerpts from the Interview

Tracks 2-4

DR LOVE: How do you think through initial treatment options for patients with mesothelioma, particularly the issue of surgery?

DR TSAO: We typically offer 2 types of surgery. The first is an extrapleural pneumonectomy. This is a massive procedure for which probably 20 out of 100 patients are candidates, but it is undertaken with curative intent. Our surgeons remove the visceral and parietal pleura. They take out the affected lung and part of the diaphragm and pericardium, and then they reconstruct everything. They also perform a mediastinal nodal dissection. In general we do not use this approach for patients with sarcomatoid mesothelioma or for patients with mediastinal involvement of mesothelioma because outcomes for those patients after the surgery tend to be poor.

Typically, after recovering from an extrapleural pneumonectomy patients receive hemithoracic radiation therapy with either external beam or intensity-modulated radiation therapy. About 4 to 6 weeks after that we administer adjuvant cisplatin/pemetrexed if the patient did not receive any neoadjuvant chemotherapy. We use the same principle as in lung cancer, for which we recommend cisplatin instead of carboplatin for definitive intent.

The second procedure performed in the United States with definitive intent is the pleurectomy decortication. This is not considered an R0 resection because microscopic disease is left behind. With this technique, we leave the lung intact but peel off the tumor in the pleura throughout the chest. We may or may not perform a mediastinal nodal dissection.

In the past, because you couldn't radiate the intact lung after this procedure, it was often considered a purely palliative technique, but now innovative radiation therapy techniques allow us to radiate only the high-risk areas where tumor involvement was significant. We have documented cases with this procedure in which patients are disease free and experience long-term survival outcomes.

DR LOVE: How would you approach pleural effusion secondary to malignant mesothelioma?

DR TSAO: A recent article published by Rintoul and colleagues in *The Lancet* evaluated the use of video-assisted thoracoscopic partial pleurectomy (VAT-PP) versus talc pleurodesis for patients with malignant pleural mesothelioma. The authors reported no OS benefit with the use of VAT-PP in this patient population (Rintoul 2014). Even though quality of life appeared to be better at certain months with VAT-PP, my sense is that patients get a good palliative benefit from talc pleurodesis and if you can control their disease with systemic agents, they generally fare well overall.

Partial pleurectomy in this setting doesn't make a lot of sense to me because the recovery time is considerable. You can achieve a similar benefit with a talc pleurodesis and systemic chemotherapy.

DR LOVE: During the next 5 to 10 years, what do you believe will be the most successful approaches to systemic therapy for mesothelioma?

DR TSAO: I believe that the immunotherapeutic agents are critical in mesothelioma because it's an immunogenic disease. We know that PD-L1 is overexpressed, so trials evaluating the incorporation of the PD-L1 inhibitors into therapy are critical. Evidence of responses to immune checkpoint inhibitors in mesothelioma is mostly anecdotal because we don't have any trials open yet for these patients.

We are currently in the process of developing a SWOG study in the neoadjuvant setting for patients with mesothelioma to evaluate an anti-PD-L1 inhibitor in combination with chemotherapy followed by maintenance immunotherapy. These agents will also be evaluated in the metastatic setting in combination with chemotherapy.

Track 7

DR LOVE: Let's talk about NSCLC. What is your approach to first-line therapy for patients with EGFR-mutant disease? How do you choose between afatinib and erlotinib in this setting?

DR TSAO: Some data were presented at ASCO 2014 suggesting that afatinib seems to work in patients with deletion exon 19 and not so well in those with the L858R mutation (Yang 2014; [3.1]). So that's food for thought when deciding which of those 2 agents to administer in the front-line setting.

Of course, quality of life is always important. Afatinib does tend to cause a little bit more diarrhea as well as a bit more rash, but it is an irreversible inhibitor, so the

thought is that it might be more potent for those patients with EGFR deletion exon 19, which is the patient population for whom I have used afatinib up front thus far. ■

3.1

LUX-Lung 3 and LUX-Lung 6: Combined Overall Survival Analysis of Phase III Studies of Afatinib versus Chemotherapy as Up-Front Therapy for Patients with Advanced Non-Small Cell Lung Cancer Harboring Common EGFR Mutations

Patient group	Afatinib (n = 419)	Chemotherapy (n = 212)
Common mutations: del(19)/L858R Median OS	27.3 mo	24.3 mo
Hazard ratio (*p*-value)	0.81 (0.0374)	
	(n = 236)	(n = 119)
Del(19) subgroup Median OS	31.7 mo	20.7 mo
Hazard ratio (*p*-value)	0.59 (0.0001)	
	(n = 183)	(n = 93)
L858R subgroup Median OS	22.1 mo	26.9 mo
Hazard ratio (*p*-value)	1.25 (0.1600)	

OS = overall survival

Conclusion: This pooled analysis reveals that first-line afatinib significantly improves OS in patients with advanced non-small cell lung cancer harboring common EGFR mutations — del(19)/L858R — compared to chemotherapy.

Yang JCH et al. *Proc ASCO* 2014;**Abstract 8004**.

SELECT PUBLICATIONS

Chance WW et al. **Hemithoracic intensity modulated radiation therapy after pleurectomy/decortication for malignant pleural mesothelioma: Toxicity, patterns of failure, and a matched survival analysis.** *Int J Radiat Oncol Biol Phys* 2014;[Epub ahead of print].

Christoph DC, Eberhardt WE. **Systemic treatment of malignant pleural mesothelioma: New agents in clinical trials raise hope of relevant improvements.** *Curr Opin Oncol* 2014;26(2):171-81.

Gomez D, Tsao AS. **Local and systemic therapies for malignant pleural mesothelioma.** *Curr Treat Options Oncol* 2014;15(4):683-99.

Opitz I. **Management of malignant pleural mesothelioma — The European experience.** *J Thorac Dis* 2014;6(Suppl 2):238-52.

Pinton G et al. **Therapies currently in Phase II trials for malignant pleural mesothelioma.** *Expert Opin Investig Drugs* 2013;22(10):1255-63.

Rintoul RC et al. **Efficacy and cost of video-assisted thoracoscopic partial pleurectomy versus talc pleurodesis in patients with malignant pleural mesothelioma (MesoVATS): An open-label, randomised, controlled trial.** *Lancet* 2014;384(9948):1118–27.

Riquelme E et al. **Frequent coamplification and cooperation between C-MYC and PVT1 oncogenes promote malignant pleural mesothelioma.** *J Thorac Oncol* 2014;9(7):998-1007.

Sequist L et al. **First-in-human evaluation of CO-1686, an irreversible, highly selective tyrosine kinase inhibitor of mutations of EGFR (activating and T790M).** *Proc ASCO* 2014;**Abstract 8010**.

Tsao AS et al. **Elevated PDGFRB gene copy number gain is prognostic for improved survival outcomes in resected malignant pleural mesothelioma.** *Ann Diagn Pathol* 2014;18(3):140-5.

Yang JCH et al. **Overall survival (OS) in patients (pts) with advanced non-small cell lung cancer (NSCLC) harboring common (del19/L858R) epidermal growth factor receptor mutations (EGFR mut): Pooled analysis of two large open-label phase III studies (LUX-Lung 3 [LL3] and LUX-Lung 6 [LL6]) comparing afatinib with chemotherapy (CT).** *Proc ASCO* 2014;**Abstract 8004**.

INTERVIEW

Naiyer A Rizvi, MD

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

Tracks 1-9

Select Excerpts from the Interview

Track 1

DR LOVE: What do we currently know about predictors of response for immune checkpoint inhibitors in lung cancer, and how does PD-L1 positivity tie in with response to anti-PD-1 treatment?

DR RIZVI: Predictors of response are becoming increasingly helpful. Smoking history is emerging as somewhat of a useful predictor in that smokers seem more likely to respond (Soria 2013). The main predictor that we're trying to understand is expression of PD-L1 (Garon 2014; Horn 2013). The notion is that if you have high levels of PD-L1, that means that you have a lot of inhibition of T cells within that tumor microenvironment and that may correlate with how dependent that tumor is on PD-1 inhibition.

For clinical trials administering an immune checkpoint inhibitor as first-line treatment for lung cancer, the bar is higher because the patients are more chemo-responsive. You want to enrich for likelihood of response, and I believe that the data that have been presented were favorable in terms of response rate with anti-PD-1 agents as first-line therapy for patients with PD-L1-positive disease (Garon 2014; Gettinger 2014; [4.1]). Both pembrolizumab and nivolumab are being studied in Phase III randomized trials as first-line therapy for patients with PD-L1-positive NSCLC (4.2).

4.1

Antitumor Activity of Anti-PD-1 Agents as First-Line Therapy for Advanced Non-Small Cell Lung Cancer

	Pembrolizumab[1] (n = 45)	Nivolumab[2] (n = 20)
Overall response rate	26%	30%
Median OS	Not reached	Not reached
6-month OS	86%	Not reported
12-month OS	Not reported	75%
Median PFS	27 weeks	Nonsquamous: 47.2 weeks Squamous: 15.1 weeks
24-week PFS	51%	60%

OS = overall survival; PFS = progression-free survival

[1] Garon EB et al. *Proc ESMO* 2014;**Abstract LBA43**; [2] Gettinger SN et al. *Proc ASCO* 2014;**Abstract 8024**.

4.2

Select Ongoing Phase III Trials of PD-1/PD-L1 Checkpoint Inhibitors in Non-Small Cell Lung Cancer (NSCLC)

Study	Target Accrual	Setting	Randomization
Checkmate 017	264 (closed)	Stage IIIB/IV squamous cell NSCLC after platinum-based chemotherapy	Nivolumab versus docetaxel
Checkmate 057	574 (closed)	Stage IIIB/IV nonsquamous cell NSCLC after platinum-based chemotherapy	Nivolumab versus docetaxel
Checkmate 026	495	Untreated Stage IV EGFR mutation-/ALK-, PD-L1+ NSCLC	Nivolumab versus investigator's choice of chemotherapy
Keynote 010	920	Previously treated PD-L1+ NSCLC	Low or high dose of pembrolizumab versus docetaxel
Keynote 024	300	Previously untreated Stage IV EGFR mutation-/ALK-, PD-L1+ NSCLC	Pembrolizumab versus platinum-based chemotherapy
Keynote 042	1,240	Previously untreated EGFR mutation-/ALK-, PD-L1+ advanced/metastatic NSCLC	Pembrolizumab versus platinum-based chemotherapy

www.clinicaltrials.gov. Accessed November 2014.

When you move to clinical trials in the second-line setting, in which response rates with chemotherapy are in the vicinity of 10%, or third-line therapy, with which activity is even lower, I believe that the requirement for PD-L1 positivity will be less, because if you have a comparable response rate or potentially even a better response rate as second- or third-line therapy, even if the disease is PD-L1-negative, there will be a lot of interest in using these agents. It's much more difficult to develop resistance to immunotherapy than with chemotherapy or targeted therapy, so we are seeing longer-term durable benefits in that subset of patients who experience a response.

Tracks 4-5

DR LOVE: Would you discuss the difference between anti-PD-1 agents and anti-PD-L1 agents and what is known about the relative efficacy and tolerability of these 2 strategies?

DR RIZVI: It's difficult to compare the agents because they are quite different. The response rates for unselected patients seem fairly comparable. Globally, the toxicities are low with all of these agents. Most patients don't feel that they're experiencing any side effects.

The most frequent toxicities include mild instances of pruritus, rash, myalgias and fatigue. We need to monitor these patients carefully for endocrine dysfunction in terms of their thyroid function test or, if patients are developing any symptoms of adrenal insufficiency, monitor their ACTH and cortisol levels. Thyroid function abnormalities are common. Adrenal insufficiency is fairly uncommon. But you have to be alert to these possibilities and introduce replacement thyroid hormone as needed. We don't see much colitis and transaminase elevation like we do with anti-CTLA-4 therapy.

The PD-L1 inhibitors might carry less risk of pneumonitis, which is something that people using these agents need to be mindful of. I have a low threshold to order a noncontrast chest CT scan for patients who develop increasing cough, shortness of breath or may be desaturating a bit on their oxygen saturation measures to ensure that we're not dealing with pneumonitis.

It's also important to note that if you observe radiologic abnormalities, they do not need to be bilateral like those we see with typical drug toxicities and bilateral inflammation. Often you may see only patchy infiltrate in the left or right lower lobe. The key is to act on those findings quickly, usually by managing with corticosteroids. We typically admit patients who are more sick or who are developing hypoxia to administer high-dose steroids.

We also allow for a longer tapering course of therapy than we would for perhaps radiation-related pneumonitis or chemotherapy-related pneumonitis, because T cells continue to be active, even without therapy, for a longer period of time. We taper treatment for these patients slowly and are alert to recrudescence of pneumonitis when the agent is stopped. By and large, we're fairly leery of re-treatment for those patients who develop pneumonitis on immunotherapy.

Track 7

DR LOVE: What are your thoughts on combining immunotherapies with other systemic agents in NSCLC?

DR RIZVI: We love that patients achieve a 15% to 20% response rate and durable responses with single-agent immune checkpoint inhibitor therapy, but we are also excited about the combination trials. Some of these include combining anti-CTLA-4 and anti-PD-1 or anti-PD-L1 agents. Trials are under way evaluating ipilimumab and nivolumab (Antonia 2014; [4.3]) in addition to tremelimumab and MEDI4736 (Pinder 2014). I consider immunotherapy similar to where we were 30 years ago with cisplatin as a backbone therapy, and with time we've been able to build on it and do better. The benefits of adding therapy may not be incremental, but hopefully they'll be bigger.

4.3

Interim Results of a Phase I Trial of Nivolumab (N) with Ipilimumab (I) as First-Line Therapy for Advanced Non-Small Cell Lung Cancer (NSCLC)*

	N 1 mg/kg + I 3 mg/kg		N 3 mg/kg + I 1 mg/kg	
	Nonsquamous (n = 15)	Squamous (n = 9)	Nonsquamous (n = 16)	Squamous (n = 9)
ORR	13%	11%	13%	33%
Stable disease	33%	22%	25%	56%

- Any-grade treatment-related adverse events (AEs) reported in 88% of patients
- Grade 3 or 4 treatment-related AEs reported in 49% of patients
- AEs led to discontinuation of treatment in 35% of patients
- Treatment-related deaths included respiratory failure (n = 1), bronchopulmonary hemorrhage (n = 1) and toxic epidermal necrolysis (n = 1).

* Patients with chemotherapy-naïve nonsquamous or squamous NSCLC (n = 49) received the 3+1 mg/kg or the 1+3 mg/kg combination dose, q3w IV for 4 cycles followed by nivolumab 3 mg/kg q2w IV until disease progression or unacceptable toxicity.

ORR = overall response rate

Antonia SJ et al. *Proc ASCO* 2014;**Abstract 8023**.

The list is growing in terms of potential combination immunotherapies and also combinations of immunotherapy with small molecules. We also presented data on the combination of erlotinib and nivolumab at ASCO 2014 and reported an approximately 20% durable response rate in patients with EGFR-mutant advanced NSCLC (Rizvi 2014).

Patients who are never smokers typically don't respond as well to checkpoint inhibitors. Patients with EGFR mutations are typically never smokers, but it's possible that the combination or possible upregulation of PD-L1 by erlotinib in acquired resistance may be a patient population in which we can use these TKIs and antibodies in combination effectively. ■

SELECT PUBLICATIONS

Antonia SJ et al. **Nivolumab (anti-PD-1; BMS-936558, ONO-4538) and ipilimumab in first-line NSCLC: Interim phase I results.** *Proc ASCO* 2014;**Abstract 8023**.

Garon EB et al. **Antitumor activity of pembrolizumab (Pembro; MK-3475) and correlation with programmed death ligand 1 (PD-L1) expression in a pooled analysis of patients with advanced NSCLC.** *Proc ESMO* 2014;**Abstract LBA43**.

Gettinger SN et al. **First-line nivolumab (anti-PD-1; BMS-936558, ONO-4538) monotherapy in advanced NSCLC: Safety, efficacy, and correlation of outcomes with PD-L1 status.** *Proc ASCO* 2014;**Abstract 8024**.

Horn L et al. **An analysis of the relationship of clinical activity to baseline EGFR status, PD-L1 expression and prior treatment history in patients with non-small cell lung cancer (NSCLC) following PD-L1 blockade with MPDL3280A (anti-PDL1).** *Proc WCLC* 2013;**Abstract MO18.01**.

Pinder MC et al. **A phase 1b open-label study to evaluate the safety and tolerability of MEDI4736, an anti–PD-L1 antibody, in combination with tremelimumab in subjects with advanced non–small cell lung cancer.** *Proc ASCO* 2014;**Abstract e19137**.

Rizvi NA et al. **Safety and clinical activity of MK-3475 as initial therapy in patients with advanced non-small cell lung cancer (NSCLC).** *Proc ASCO* 2014;**Abstract 8007**.

Soria JC et al. **Clinical activity, safety and biomarkers of PD-L1 blockade in non-small cell lung cancer (NSCLC): Additional analyses from a clinical study of the engineered antibody MPDL3280A (anti-PDL1).** *Proc ECC* 2013;**Abstract 3408**.

QUESTIONS (PLEASE CIRCLE ANSWER):

1. **Side effects associated with the third-generation, irreversible EGFR TKI rociletinib include _____.**
   a. Diarrhea
   b. Nausea
   c. Hyperglycemia
   d. All of the above

2. **A Phase Ib trial of the combination of afatinib and cetuximab for patients with EGFR mutation-positive NSCLC and acquired resistance to erlotinib or gefitinib demonstrated _____.**
   a. Similar confirmed response rates between patients with and without EGFR T790M mutations
   b. Similar PFS for the T790M-positive and T790M-negative cohorts
   c. Both a and b

3. **The ongoing Phase III ALEX study is comparing alectinib to crizotinib in patients with treatment-naïve ALK-positive advanced NSCLC.**
   a. True
   b. False

4. **The Phase I ASCEND-1 trial demonstrated an intracranial response rate of 40% with ceritinib in patients with ALK-rearranged NSCLC and brain metastases.**
   a. True
   b. False

5. **In a pooled exploratory analysis of the Phase III PointBreak and ECOG-E4599 trials by patient age, a statistically significant survival benefit associated with the addition of bevacizumab to paclitaxel/carboplatin was reported in which of the following patient subgroups?**
   a. Patients <65 years old
   b. Patients aged 65 to 75
   c. Patients ≥75 years old
   d. Both a and b
   e. All of the above

6. **An article published in *The Lancet* by Rintoul and colleagues reported an OS benefit associated with the use of video-assisted thoracoscopic partial pleurectomy in comparison to talc pleurodesis for patients with malignant pleural mesothelioma.**
   a. True
   b. False

7. **A combined analysis of the LUX-Lung 3 and LUX-Lung 6 Phase III trials of first-line therapy failed to demonstrate an OS benefit with afatinib versus chemotherapy in patients with advanced NSCLC who were positive for the EGFR del(19) mutation.**
   a. True
   b. False

8. **Adverse events commonly associated with anti-PD-1/anti-PD-L1 immune checkpoint inhibitors include _____.**
   a. Fatigue
   b. Myalgia
   c. Pruritus
   d. Rash
   e. All of the above

9. **Trials evaluating the anti-PD-1 agents nivolumab and pembrolizumab have reported overall response rates of approximately 30% for patients receiving either of these 2 agents as first-line therapy for advanced NSCLC.**
   a. True
   b. False

10. **Interim results of a Phase I trial evaluating the combination of nivolumab and ipilimumab as first-line therapy for advanced NSCLC suggest that the combination provides benefit for patients with _____ histology.**
    a. Nonsquamous
    b. Squamous
    c. Both a and b
    d. Neither a nor b

EDUCATIONAL ASSESSMENT AND CREDIT FORM

Lung Cancer Update — Issue 3, 2014

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

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

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

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

	BEFORE	AFTER
Incidence and management of treatment-associated hyperglycemia with the third-generation, irreversible EGFR TKI rociletinib (CO-1686)	4 3 2 1	4 3 2 1
Differential activity of first- and second-generation ALK inhibitors for patients with NSCLC and brain metastases	4 3 2 1	4 3 2 1
Efficacy of anti-PD-1 agents alone or in combination with ipilimumab as first-line therapy for patients with advanced NSCLC	4 3 2 1	4 3 2 1
Management of checkpoint inhibitor-associated pneumonitis	4 3 2 1	4 3 2 1
Results of a pooled analysis of the PointBreak and ECOG-E4599 trials by patient age (addition of bevacizumab to carboplatin/paclitaxel as first-line therapy for nonsquamous NSCLC)	4 3 2 1	4 3 2 1
Surgical approaches with curative intent and novel therapeutic strategies (eg, immune checkpoint blockade) in mesothelioma	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:

- 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 mutations. .....4 3 2 1 N/M N/A
- Recall the scientific rationale for the 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
- 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
- Describe mechanisms of tumor resistance to EGFR tyrosine kinase inhibitors, and identify investigational therapeutic opportunities to circumvent this process. .....4 3 2 1 N/M N/A
- Develop an evidence-based approach to the selection of induction and maintenance biologic therapy and/or chemotherapy for patients with advanced non-small cell lung cancer. .....4 3 2 1 N/M N/A
- Consider the use of multimodality therapy for appropriate patients with mesothelioma who may potentially be cured with this approach. .....4 3 2 1 N/M N/A

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.....

Would you recommend this activity to a colleague?

☐ Yes ☐ No

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.....

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

Faculty	Knowledge of subject matter	Effectiveness as an educator
D Ross Camidge, MD, PhD	4 3 2 1	4 3 2 1
Corey J Langer, MD	4 3 2 1	4 3 2 1
Anne S Tsao, MD	4 3 2 1	4 3 2 1
Naiyer A Rizvi, 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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