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

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FACULTY INTERVIEWS

Joel W Neal, MD, PhD
Paul K Paik, MD
Leora Horn, MD, MSc
Edward B Garon, MD, MS

EDITOR

Neil Love, MD

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2 Audio CDs
Monograph
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 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, BRAF-ALK gene fusions, RAS1 gene rearrangements and other recently identified driver mutations—and the approved and investigational treatment options for patients with these mutations.
• Formulate a rational approach for molecular testing of tumors in order to identify potential protocol and off-protocol treatment options for patients.
• Describe mechanisms of tumor resistance to EGFR tyrosine kinase inhibitors, and identify investigational therapeutic opportunities to circumvent this process.
• Develop an evidence-based approach for the selection of induction and maintenance biologic therapy and/or chemotherapy for patients with advanced non-small cell lung cancer.
• Recall the scientific rationale for ongoing investigation of novel agents or immunotherapeutic approaches in lung cancer, and counsel appropriately selected patients about study participation.

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FACULTY — The following faculty (and their spouses/partners) reported real or apparent conflicts of interest, which have been resolved through a conflict of interest resolution process:

Dr Neal — Contracted Research: ArQule Inc, Genentech BioOncology, Merck. Dr Paik — Advisory Committee: Celgene Corporation; Contracted Research: AstraZeneca Pharmaceuticals LP, Bristol-Myers Squibb Company, GlaxoSmithKline. Dr Horn — Advisory Committee: Bristol-Myers Squibb Company, Clovis Oncology, Helix BioPharma Corp, Puma Biotechnology Inc; Consulting Agreements: Bayer HealthCare Pharmaceuticals, Merck; Contracted Research: Astellas; Honoraria: Boehringer Ingelheim Pharmaceuticals Inc. Dr Garon — Consulting Agreement: Boehringer Ingelheim Pharmaceuticals Inc; Contracted Research: AstraZeneca Pharmaceuticals LP, Genentech BioOncology, ImClone Systems, a wholly owned subsidiary of Eli Lilly and Company, Lilly, Merck, Novartis Pharmaceuticals Corporation, Pfizer Inc, Puma Biotechnology Inc.

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Select Excerpts from the Interview

Tracks 1-2

**DR LOVE:** The results of the Phase III RADIANT trial of 2 years of adjuvant erlotinib versus placebo in patients with EGFR–positive non–small cell lung cancer (NSCLC) were reported at ASCO 2014. No survival benefit was reported overall with erlotinib, but in a previously unspecified subset of 161 patients with activating EGFR mutations, disease-free survival increased from 28.5 to 46.4 months (Kelly 2014; [1.1]). What are your thoughts on this study?

**DR NEAL:** When the RADIANT trial was developed, it wasn’t known if EGFR mutations were important predictors of response for patients receiving erlotinib. RADIANT was designed to enroll patients with EGFR–positive NSCLC as determined by either immunohistochemistry (IHC) or FISH analysis. Now that we know a lot more about EGFR tyrosine kinase inhibitors (TKIs), these enrollment criteria may...
have little to do with responsiveness to erlotinib. EGFR amplification by FISH seems to correlate somewhat with the presence of EGFR mutations. IHC positivity occurs across many lung cancers, and I don’t believe it’s particularly predictive of response to EGFR TKIs. In the RADIANT trial, an improvement in 2-year disease-free survival with erlotinib was observed in the subset of patients who had EGFR mutations.

DR LOVE: Would you also discuss the updated results of the Phase II single-arm SELECT trial of adjuvant erlotinib in resected early-stage EGFR-mutant NSCLC (Pennell 2014)?

DR NEAL: The results for all 100 patients on the SELECT trial were presented at ASCO 2014. We observed a 2-year disease-free survival of 89% across multiple disease stages. A 2-year disease-free survival of 89% is impressive in lung cancer, regardless of the subset. These results are consistent with the results of the RADIANT EGFR-mutant subgroup analysis.

Track 6

DR LOVE: What is the current status of the third-generation EGFR inhibitors in lung cancer?

DR NEAL: Studies of 3 of these inhibitors, CO-1686, AZD-9291 and HM61713, were presented at ASCO 2014. These agents belong to a slightly different class than erlotinib and afatinib in that they have minimal activity against wild-type EGFR.
They induce minimal rash and diarrhea but exhibit specific activity against sensitizing EGFR mutations such as exon 19 deletion and L858R. They are active against disease with acquired resistance to TKIs in the form of the T790M mutations, which occur in approximately 50% of NSCLC with acquired resistance.

We don’t know whether one of these agents is better than the others. Each has a different side-effect profile. CO-1686 is associated with hyperglycemia, and AZD-9291 was associated with a low incidence of interstitial lung disease. HM61713, which was used at a much lower dose, demonstrated a lower response rate of approximately 30% in patients with T790M EGFR mutations, but we have not yet seen its effects at the maximum tolerated dose (Kim 2014). For AZD-9291 (Janne 2014) or CO-1686 (Sequist 2014), the response rate was more than 60%. I believe these agents may be more tolerable for longer periods in the adjuvant setting. They hold promise in the first-line treatment of advanced EGFR–mutant NSCLC.

Track 8

DR LOVE: What is your view on the utility of the VeriStrat proteomic assay and the results of the Phase III PROSE trial (Gregorc 2014; [1.2])?

DR NEAL: The prospective PROSE study investigated the role of an EGFR TKI in all patients, not just those with EGFR mutations. The VeriStrat assay is a mass spectrometry–based serum marker assay that categorizes patients with active cancer into a poor or good prognostic group.

It’s currently impossible to predict who will respond to EGFR TKI therapy from the tumor tissue. For example, it is not known whether a man who is an active smoker with squamous cell disease will respond to erlotinib therapy, even though it is FDA approved as second- and third-line therapy for that patient. As a result, the VeriStrat assay is trying to tease out those for whom erlotinib should be used.

The PROSE study indicated that patients in the VeriStrat good group seemed to perform better with erlotinib than the VeriStrat poor patient subset. I believe that the overall enthusiasm for using erlotinib in the second-, third- or fourth-line setting has diminished considerably since its initial introduction in 2004. Erlotinib is still perfectly appropriate in the second- and probably the third-, fourth- and fifth-line setting, regardless of what the VeriStrat assay shows. Once a patient has received chemotherapy several times up to the fourth line, I believe a TKI is a reasonable next option. My personal practice hasn’t been to order the VeriStrat assay, although it seems to be prognostically useful.

1.2

<table>
<thead>
<tr>
<th>Phase III PROSE Trial: Predictive Value of the VeriStrat Proteomic Signature in Non-Small Cell Lung Cancer Treated with Second-Line Erlotinib or Chemotherapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median overall survival</td>
</tr>
<tr>
<td>-------------------------</td>
</tr>
<tr>
<td>All patients (n = 134, 129)</td>
</tr>
<tr>
<td>VeriStrat good (n = 96, 88)</td>
</tr>
<tr>
<td>VeriStrat poor (n = 38, 41)</td>
</tr>
</tbody>
</table>

DR LOVE: What are your thoughts on the results of the trial of erlotinib with or without bevacizumab for patients with nonsquamous NSCLC with activating EGFR mutations (Kato 2014; [1.3])?

DR NEAL: The progression-free survival (PFS) with erlotinib was 9.7 months, but in combination with bevacizumab it was 16 months. A similar trial is ongoing in the United States (NCT01562028). It’s possible that the angiogenic signal from EGFR-mutant lung cancer is rather monotone and may be VEGF driven. Perhaps those are the patients who should receive bevacizumab, possibly with erlotinib. Extrapolating from these results, maybe these patients should receive bevacizumab whenever they receive chemotherapy, whether in the second line or beyond. This would be more in line with standard treatment.

<table>
<thead>
<tr>
<th>Randomized Trial of Erlotinib (ERL) and Bevacizumab (Bev) versus ERL Alone as First-Line Therapy for Advanced EGFR Mutation-Positive Nonsquamous Non-Small Cell Lung Cancer</th>
</tr>
</thead>
<tbody>
<tr>
<td>All patients</td>
</tr>
<tr>
<td>Median PFS</td>
</tr>
<tr>
<td>Objective response rate</td>
</tr>
<tr>
<td>Disease control rate</td>
</tr>
<tr>
<td>PFS by EGFR mutation type</td>
</tr>
<tr>
<td>Exon 19 deletion (n = 40, 40)</td>
</tr>
<tr>
<td>Exon 21 L858R (n = 35, 37)</td>
</tr>
<tr>
<td>Select adverse events</td>
</tr>
<tr>
<td>All grades</td>
</tr>
<tr>
<td>Rash</td>
</tr>
<tr>
<td>Hypertension</td>
</tr>
<tr>
<td>Proteinuria</td>
</tr>
<tr>
<td>Hemorrhagic events</td>
</tr>
</tbody>
</table>

PFS = progression-free survival; NR = not reported


SELECT PUBLICATIONS


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 2014;Abstract 8011.

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

Tracks 1-15

Track 1  Treatment options for advanced squamous cell NSCLC
Track 2  Spectrum of driver oncogene mutations in biomarker-verified squamous cell lung cancer (SCC)
Track 3  SWOG-1400: Biomarker-driven master protocol for second-line therapy of SCC
Track 4  Integration of next-generation sequencing platforms into clinical practice
Track 5  Results of the Phase III SQUIRE trial of necitumumab with gemcitabine and cisplatin as first-line treatment for advanced SCC
Track 6  Risk of hemoptysis in patients with resected SCC treated with adjuvant bevacizumab
Track 7  Improved response rate with first-line nanoparticle albumin-bound (nab) paclitaxel and carboplatin compared to standard solvent-based paclitaxel and carboplatin in advanced SCC of the lung
Track 8  Incidence of BRAF mutations in NSCLC
Track 9  Potential actionable targets in small cell lung cancer
Track 10 Second opinion: Therapeutic approach for a 76-year-old patient with Stage IV EGFR-mutant adenocarcinoma with bilateral lung nodules and pleural involvement
Track 11 Management of erlotinib-associated dermatologic toxicities
Track 12 Pooled analysis of the Phase III LUX-Lung 3 and LUX-Lung 6 trials of afatinib versus chemotherapy: Overall survival in patients with advanced NSCLC harboring common — del(19)/L858R — EGFR mutations
Track 13 Results of REVEL: A Phase III study of docetaxel with or without ramucirumab as second-line therapy for Stage IV NSCLC after disease progression on 1 prior platinum-based therapy
Track 14 Case discussion: An 80-year-old patient with Stage IV SCC with basaloid features and mutations in the hedgehog signaling pathway
Track 15 Case discussion: A 69-year-old former smoker with Stage IV SCC with suspected synchronous bilateral primary tumors

Select Excerpts from the Interview

Tracks 2-3

DR LOVE: What is known about the biology of squamous cell carcinoma (SCC) of the lung, particularly in relation to genetic mutations?

DR PAIK: SCC is distinct from adenocarcinoma at a biologic level. Genotype data generated by the Cancer Genome Atlas and other centers demonstrate that EGFR mutations, ALK rearrangements, ROS1 fusions and RET fusions don’t occur in SCC. KRAS mutations are also uncommon, probably occurring at a frequency of 1% to 2% (Rekhtman 2012).
We have found, though, that FGFR1 amplification and PI3 kinase pathway changes are fairly common in SCC. These 2 alterations alone are probably present in approximately 50% of SCC.

DR LOVE: Would you explain the Lung Cancer Master Protocol (Lung-MAP) in SCC and discuss your thoughts on it?

DR PAIK: This initiative being spearheaded by SWOG is a multicenter clinical trial protocol providing patients with SCC access to logical and rational trials in order to validate potential therapeutic targets (2.1). Every patient will be centrally genotyped. Based on their genotype, patients will be enrolled on trials evaluating agents targeted against their specific genetic alterations. Patients who test negative for the specific mutations will be enrolled on a trial investigating an agent targeted against the PD-1/PD-L1 axis. All the trials are randomized against docetaxel as the standard second-line therapy. These trials are not set in stone and will be adaptable depending on future results.

2.1 Lung-MAP Trial: S1400 Phase II/III Biomarker-Driven Master Protocol for Second-Line Therapy of Squamous Cell Lung Cancer

<table>
<thead>
<tr>
<th>Positive test result</th>
<th>Trial assignment</th>
</tr>
</thead>
<tbody>
<tr>
<td>PI3KCA gene mutation</td>
<td>GDC-0032 versus docetaxel</td>
</tr>
<tr>
<td>CCND1, CCND2, CCND3 or CDK4/6 gene amplification</td>
<td>Palbociclib versus docetaxel</td>
</tr>
<tr>
<td>FGFR gene amplification, mutation or fusion</td>
<td>AZD4547 versus docetaxel</td>
</tr>
<tr>
<td>High protein levels of c-MET</td>
<td>Rilotumumab + erlotinib versus erlotinib</td>
</tr>
<tr>
<td>None of the above mutations</td>
<td>MEDI4736 versus docetaxel</td>
</tr>
</tbody>
</table>

**Primary objectives:** Progression-free survival by RECIST 1.1 (Phase II); overall survival (Phase III)


Track 5

DR LOVE: What are your thoughts on the results of the Phase III SQUIRE trial, which were recently presented at ASCO 2014?

DR PAIK: The SQUIRE trial randomly assigned patients with Stage IV SCC to first-line cisplatin/gemcitabine with or without the EGFR antibody necitumumab. The primary endpoint of overall survival (OS) was met, with the addition of necitumumab leading to an improvement from 9.9 months to 11.5 months (Thatcher 2014; [2.2]). However, PFS and response rates were not consistent with the OS result and would suggest that the therapy, at least while patients were receiving it, was not better than placebo and that the benefit was manifested later in terms of survival. Based on the modest survival benefit with necitumumab, the questions arise, is this clinically meaningful and should we support its approval?
The dermatologic toxicity is similar to that observed with cetuximab, so whether we will observe an increase in toxicity is another issue. If necitumumab is approved, the toxicity and the modest survival benefit must be discussed with the patient.

### SQUIRE: 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

<table>
<thead>
<tr>
<th></th>
<th>Gem/cis + necitumumab <em>(n = 545)</em></th>
<th>Gem/cis <em>(n = 548)</em></th>
<th>Hazard ratio</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median OS</td>
<td>11.5 mo</td>
<td>9.9 mo</td>
<td>0.84</td>
<td>0.012</td>
</tr>
<tr>
<td>Median PFS</td>
<td>5.7 mo</td>
<td>5.5 mo</td>
<td>0.85</td>
<td>0.020</td>
</tr>
<tr>
<td>ORR</td>
<td>31.2%</td>
<td>28.8%</td>
<td>—</td>
<td>0.400</td>
</tr>
</tbody>
</table>

Select Grade ≥ 3 adverse events

<table>
<thead>
<tr>
<th></th>
<th>Gem/cis + necitumumab <em>(n = 538)</em></th>
<th>Gem/cis <em>(n = 541)</em></th>
</tr>
</thead>
<tbody>
<tr>
<td>Neutropenia</td>
<td>24.3%</td>
<td>27.5%</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>10.2%</td>
<td>10.7%</td>
</tr>
<tr>
<td>Hypomagnesemia</td>
<td>9.3%</td>
<td>1.1%</td>
</tr>
<tr>
<td>Skin rash</td>
<td>7.1%</td>
<td>0.4%</td>
</tr>
<tr>
<td>Venous thromboembolic events*</td>
<td>5.0%</td>
<td>2.6%</td>
</tr>
</tbody>
</table>

OS = overall survival; PFS = progression-free survival; ORR = overall response rate
* Fatal events, n (%): Gem/cis + necitumumab = 1 (0.2%); gem/cis = 1 (0.2%)


### Track 7

**DR LOVE:** Would you comment on your current algorithm for first- and second-line treatment of SCC and where, if at all, nanoparticle albumin-bound (*nab*) paclitaxel fits in?

**DR PAIK:** At my institution, the de facto standard in the first-line setting is platinum and gemcitabine. However, I’m not dogmatic about the selection of first-line therapy because we don’t have head-to-head data comparing platinum/gemcitabine to other doublets. My second-line treatment choice is a taxane.

The subset analysis of the randomized Phase III trial of carboplatin and *nab* paclitaxel versus carboplatin and paclitaxel demonstrated that patients with SCC seemed to benefit in terms of response rate and PFS with *nab* paclitaxel (Socinski 2012). Based on these results, I may consider carboplatin/*nab* paclitaxel in the first-line setting for patients with SCC who are symptomatic and need a tumor response. Use of *nab* paclitaxel is also attractive in patients with taxane hypersensitivity or a contraindication to high-dose steroids used to prevent allergic reactions.

### Track 12

**DR LOVE:** I’m curious about your thoughts on afatinib and in what clinical situations you would administer it — up front instead of erlotinib or later line, for example?
DR PAIK: Afatinib, for me, is still a gray area. The combined analysis of the LUX-Lung 3 and LUX-Lung 6 trials was recently presented at ASCO 2014, and a modest OS benefit was reported with afatinib versus chemotherapy in the first-line setting (Yang 2014; [2.3]). This has not been observed before with an EGFR TKI. However, because of the issues that occur after a patient crosses over, the data are not sufficient as of yet for me to replace erlotinib as the standard.

In terms of afatinib in the acquired resistance setting, the response rate is low, about 8% (Katakami 2013). This 8% is not a true reflection of activity, as part of this response is from re-treatment effects — patients who have been off TKI therapy and then resumed treatment and experienced a response.

The afatinib/cetuximab data are compelling (Janjigian 2012), but the combination is associated with a fair amount of dermatologic toxicity, which is a real limitation. Owing to the toxicity, I’m reluctant to use the combination in the first-line setting.

### SELECT PUBLICATIONS

Janjigian YY et al. Activity of afatinib/cetuximab in patients (pts) with EGFR mutant non-small cell lung cancer (NSCLC) and acquired resistance (AR) to EGFR inhibitors. *Proc ESMO 2012; Abstract 12270*.


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### 2.3 LUX-Lung 3 and LUX-Lung 6: Combined Overall Survival Analysis of Phase III Studies of Afatinib versus Chemotherapy in EGFR Mutation-Positive Advanced Non-Small Cell Lung Cancer

<table>
<thead>
<tr>
<th>Patient group</th>
<th>Afatinib (n = 419)</th>
<th>Chemotherapy (n = 212)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Common mutations: del(19)/L858R</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median OS</td>
<td>27.3 mo</td>
<td>24.3 mo</td>
</tr>
<tr>
<td>Hazard ratio (p-value)</td>
<td>0.81 (0.0374)</td>
<td></td>
</tr>
<tr>
<td>(n = 236)</td>
<td>(n = 119)</td>
<td></td>
</tr>
<tr>
<td>Del(19) subgroup</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median OS</td>
<td>31.7 mo</td>
<td>20.7 mo</td>
</tr>
<tr>
<td>Hazard ratio (p-value)</td>
<td>0.59 (0.0001)</td>
<td></td>
</tr>
<tr>
<td>(n = 183)</td>
<td>(n = 93)</td>
<td></td>
</tr>
<tr>
<td>L858R subgroup</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median OS</td>
<td>22.1 mo</td>
<td>26.9 mo</td>
</tr>
<tr>
<td>Hazard ratio (p-value)</td>
<td>1.25 (0.1600)</td>
<td></td>
</tr>
<tr>
<td>OS = overall survival</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Yang JCH et al. *Proc ASCO 2014; Abstract 8004.*
### Tracks 1-12

| Track 1 | Immune checkpoint blockade strategies — CTLA4 inhibition, anti-PD-1 and anti-PD-L1 monoclonal antibodies |
| Track 2 | Mechanisms of action of anti-PD-1 and anti-PD-L1 antibodies |
| Track 3 | Anti-PD-1-associated pneumonitis and colitis |
| Track 4 | **Case discussion:** An 85-year-old patient with EGFR and ALK wild-type, KRAS mutation-positive metastatic adenocarcinoma of the lung experiences a considerable response to nivolumab on a clinical trial before discontinuing therapy because of an allergic reaction |
| Track 5 | Investigation of the novel ALK inhibitor X-396 in patients with advanced solid tumors |
| Track 6 | Mechanisms of action of approved and novel ALK inhibitors in NSCLC |
| Track 7 | **Case discussion:** A former smoker who previously received treatment 8 years ago for Stage IV adenocarcinoma of the lung and is now undergoing X-396 therapy for crizotinib-resistant disease |
| Track 8 | Efficacy of second-generation ALK inhibitors in crizotinib-resistant, ALK-positive NSCLC with CNS metastases |
| Track 9 | **Case discussion:** A 59-year-old former smoker who received adjuvant cisplatin/pemetrexed for Stage IIIA adenocarcinoma with an EGFR exon 19 deletion |
| Track 10 | Tolerability of novel third-generation EGFR inhibitors |
| Track 11 | Acquired resistance of EGFR-mutant adenocarcinoma of the lung to afatinib/cetuximab is associated with activation of mTORC1 |
| Track 12 | Dealing with stress and burnout in the practice of oncology |

### Select Excerpts from the Interview

**Tracks 1-3**

**DR LOVE:** What are your thoughts on the emerging data with immune checkpoint inhibitors for the treatment of lung cancer?

**DR HORN:** Inhibitors of immune checkpoint pathways are changing the way we think about immunotherapy in lung cancer. Ipilimumab, an antibody to CTLA4, has demonstrated promising results in combination with chemotherapy.

Phase II trials investigating the addition of ipilimumab to chemotherapy in both small cell lung cancer (SCLC) and NSCLC have demonstrated encouraging results with a phased regimen of chemotherapy followed by ipilimumab and chemotherapy (Reck 2013; Lynch 2012). Two large Phase III trials in SCLC and NSCLC evaluating this regimen of ipilimumab and chemotherapy versus chemotherapy have recently closed, and we’re awaiting those results.
I believe that PD-1/PD-L1 inhibitors are some of the most exciting drugs that we have in lung cancer currently. In contrast to CTLA4 inhibitors, they have single-agent activity. So the toxicities from chemotherapy can be eliminated with these agents. The response rates of around 20% to 30% are much higher than those with chemotherapy. Response rates are higher for patients whose tumors are positive for PD-L1 expression. Interestingly, however, responses are also observed in patients with tumors that are PD-L1-negative, so we don’t yet fully understand which patients will benefit most from these drugs.

What is impressive is that when these inhibitors are effective, responses are durable. Some patients on the early Phase I trials who have finished 2 years of treatment with the anti-PD-1 inhibitors have not required re-treatment more than 18 months later. This is unheard of in lung cancer.

**DR LOVE:** What is the mechanism of action of PD-1/PD-L1 inhibitors?

**DR HORN:** The interaction of PD-1 with its ligands PD-L1/L2 prevents overactivation of T cells and dampens the immune response. PD-1/PD-L1 inhibitors work in the tumor microenvironment to block this interaction and maintain T-cell activity against tumor cells.

I believe that in terms of efficacy, the PD-1 and PD-L1 inhibitors are similar. The big difference between the PD-1 and PD-L1 inhibitors is that whereas anti-PD-1 antibodies inhibit the interaction between PD-1 and its ligands PD-L1 and PD-L2, the anti-PD-L1 antibodies do not inhibit PD-L2 expressed on lung cells. The risk of pneumonitis is lower with anti-PD-L1 antibodies compared to anti-PD1 antibodies. Cases of severe or fatal pneumonitis have not been observed with the anti-PD-L1 antibodies.

**DR LOVE:** Would you comment on the side effects reported with the PD-1/PD-L1 inhibitors?

**DR HORN:** A few cases of pneumonitis have been reported with these agents. The risk of severe pneumonitis that requires intervention and therapy is less than 5%. It is important to educate patients that pneumonitis may occur. We tell patients that if they develop coughing or shortness of breath and have difficulty breathing, they should go to the emergency room. Early administration of steroids is key to managing pneumonitis. Colitis is the other severe toxicity associated with these agents, but it is not common. Early intervention is also important in managing colitis. A side effect that we have observed quite commonly is hypothyroidism, so we routinely monitor thyroid function. The toxicities with PD-1/PD-L1 inhibitors are less severe than those observed with ipilimumab. Overall, the side effects associated with these agents are easier to tolerate than those with chemotherapy.

**Track 5**

**DR LOVE:** Would you discuss the recent data with the novel second-generation ALK inhibitors?

**DR HORN:** Crizotinib is an effective ALK inhibitor but does not have good CNS penetration. It elicits about a 70% response rate in patients who have ALK-positive lung cancer, but about half of those patients will develop disease progression in the brain.
The second-generation ALK inhibitor ceritinib was recently approved for patients with ALK-positive metastatic NSCLC that is resistant to or for those who are intolerant to crizotinib. At ASCO this year, data were presented that reported a response rate of more than 50% in patients with ALK-rearranged NSCLC. What was also impressive is that ceritinib demonstrated activity in some patients with brain metastases (Kim 2014; [3.1]).

Ceritinib is associated with a fairly high rate of gastrointestinal toxicities that can affect patient quality of life. That may be significant if we see that other second-generation inhibitors that do not have the same toxicity profiles yield similar responses.

We were excited to open a Phase I trial of X-396, another second-generation ALK inhibitor. Durable responses to X-396 were observed (Horn 2014; [3.2]). The trial has only enrolled about 35 patients so far, and not all patients have ALK-positive disease. In the expansion study we are only enrolling patients with ALK-positive NSCLC.

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

<table>
<thead>
<tr>
<th>Efficacy</th>
<th>ALK inhibitor treated</th>
<th>ALK inhibitor naïve</th>
<th>Overall</th>
</tr>
</thead>
<tbody>
<tr>
<td>All patients (n = 163, 83, 246)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Overall response rate</td>
<td>54.6%</td>
<td>66.3%</td>
<td>58.5%</td>
</tr>
<tr>
<td>Complete response</td>
<td>1.2%</td>
<td>1.2%</td>
<td>1.2%</td>
</tr>
<tr>
<td>Partial response</td>
<td>53.4%</td>
<td>65.1%</td>
<td>57.3%</td>
</tr>
<tr>
<td>Patients with brain metastases at baseline (n = 98, 26, 124)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Overall response rate</td>
<td>50.0%</td>
<td>69.2%</td>
<td>54.0%</td>
</tr>
<tr>
<td>Select adverse events (n = 255)</td>
<td>Any grade</td>
<td>Grade 3/4</td>
<td></td>
</tr>
<tr>
<td>Diarrhea</td>
<td>86%</td>
<td>6%</td>
<td></td>
</tr>
<tr>
<td>Nausea</td>
<td>80%</td>
<td>4%</td>
<td></td>
</tr>
<tr>
<td>Vomiting</td>
<td>60%</td>
<td>4%</td>
<td></td>
</tr>
<tr>
<td>Fatigue</td>
<td>52%</td>
<td>5%</td>
<td></td>
</tr>
<tr>
<td>Elevated ALT</td>
<td>80%</td>
<td>27%</td>
<td></td>
</tr>
<tr>
<td>Elevated AST</td>
<td>75%</td>
<td>13%</td>
<td></td>
</tr>
</tbody>
</table>


### Track 11

- **DR LOVE:** You were part of a group that recently published a paper titled “Acquired resistance of EGFR mutant lung adenocarcinomas to afatinib plus cetuximab is associated with activation of mTORC1” (Pirrazoli 2014). Would you discuss some of the work by your colleague William Pao that led to the concept of combining afatinib and cetuximab?

- **DR HORN:** Dr Pao previously reported that the combination of afatinib and cetuximab was superior to either agent alone in mice with L858R and T790M mutations. These data led to a large Phase Ib trial of afatinib and cetuximab for patients with EGFR-mutant NSCLC and acquired resistance to EGFR TKIs. The rate of disease control and responses in both T790M-positive and T790M-negative disease was fairly high (Janjigian 2012).
The recent paper demonstrating mTORC1 as a mechanism of resistance to afatinib and cetuximab came out of a collaboration with Yale. Many were interested in determining why the combination was effective in patients with T790M-negative disease. Studies have shown that HER2 amplification is one mechanism of acquired resistance to EGFR TKIs (Takezawa 2012). This may explain the efficacy of afatinib, a HER2 inhibitor, in patients with T790M-negative disease.

Two large trials are being launched through the cooperative groups. A trial coordinated by SWOG will compare afatinib to the combination of afatinib and cetuximab as first-line therapy for patients with EGFR-mutant NSCLC. A proposed trial in the second-line setting through ECOG will compare afatinib to afatinib and cetuximab in patients with EGFR-mutant NSCLC who have acquired resistance to EGFR TKIs.

**SELECT PUBLICATIONS**

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


Takezawa K et al. HER2 amplification: A potential mechanism of acquired resistance to EGFR inhibition in EGFR-mutant lung cancers that lack the second-site EGFRT790M mutation. *Cancer Discov 2012;2(10):922.*
Dr Garon is Associate Professor at the David Geffen School of Medicine at UCLA and Director of the Thoracic Oncology Program at Jonsson Comprehensive Cancer Center in Los Angeles, California.

tracks 1-9

Track 1 REVEL: Results of a Phase III study of docetaxel and ramucirumab versus docetaxel and placebo in the second-line treatment of Stage IV NSCLC

Track 2 Activity and safety of the novel anti-PD-1 antibody pembrolizumab (MK-3475) as initial therapy for advanced NSCLC

Track 3 Clinical experience with anti-PD-1 and anti-PD-L1 antibodies

Track 4 Efficacy of checkpoint inhibitors in squamous versus nonsquamous histology

Track 5 High PD-L1 expression as a predictor of response to pembrolizumab

Track 6 Clinical experience with checkpoint inhibitor-associated pneumonitis

Track 7 Regulatory issues in approving new agents in oncology

Track 8 Results of a Phase II study of pemetrexed/carboplatin or pemetrexed/cisplatin with concurrent radiation therapy ➔ pemetrexed consolidation in Stage IIIA/B NSCLC

Track 9 Use of pemetrexed-based therapy for patients with Stage III disease

Select Excerpts from the Interview

Track 1

DR LOVE: Would you discuss the results of the Phase III REVEL trial reported at ASCO 2014?

DR GARON: The only Phase III study of ramucirumab in NSCLC to date is the REVEL trial, which randomly assigned patients with advanced squamous and nonsquamous cell disease to docetaxel with or without ramucirumab (Perol 2014; [4.1]). Interestingly, the outcomes exceeded our expectations. The control arm demonstrated a survival of 9.1 months and a response rate of 13.6%. The addition of ramucirumab led to PFS and OS benefits.

Some controversy about the results of the study revolved around the duration of benefit in that the PFS was similar to what was anticipated when the study was started. The PFS was 3 months in the control arm, and that was increased to 4.5 months with ramucirumab. Almost all of that PFS benefit translated into an OS benefit. So the 1.5-month PFS benefit was almost entirely recapitulated as 1.4 months in terms of OS.

This was controversial in the sense that a number of discussions at ASCO have taken place recently about what an appropriate clinically significant duration of survival benefit should be.
From my perspective, patients are happy about any therapy that prolongs survival. No duration of additional life would cause them to say, “That’s not enough for me to care about.” That being said, factors that should be considered when evaluating any new agent include financial costs, quality of life and toxicity. That’s a much more constructive way to evaluate the benefit of a drug overall.

Tracks 2, 5

DR LOVE: Would you review the current status of research on immune checkpoint inhibition in lung cancer?

DR GARON: The inhibition of PD-1 and PD-L1 has made a tremendous change in my practice. These agents are having significant and meaningful effects in many clinical trials. I’ve had to overhaul my entire clinic to accommodate the demand from patients for these agents.

Three agents are leading this class of drugs — nivolumab, pembrolizumab (MK-3475), formerly referred to as lambrolizumab, and MPDL3280A, an anti-PD-L1 monoclonal antibody. These agents have shown remarkably similar results with response rates of approximately 20%, largely in a population of patients who have previously received treatment. However, a Phase I study of the anti-PD-1 monoclonal antibody nivolumab demonstrated a similar response rate of approximately 20% in the front-line setting for patients with advanced NSCLC (Rizvi 2014). In all, the toxicity profile is good. I’m

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

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Ram + doc (n = 628)</th>
<th>Plac + doc (n = 625)</th>
<th>Hazard ratio</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median OS</td>
<td>10.5 mo</td>
<td>9.1 mo</td>
<td>0.857</td>
<td>0.0235</td>
</tr>
<tr>
<td>Median PFS</td>
<td>4.5 mo</td>
<td>3.0 mo</td>
<td>0.762</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>ORR</td>
<td>22.9%</td>
<td>13.6%</td>
<td>NR</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>DCR</td>
<td>64%</td>
<td>52.6%</td>
<td>NR</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Select adverse events</th>
<th>Ram + doc (n = 627)</th>
<th>Plac + doc (n = 618)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neutropenia</td>
<td>55.0%</td>
<td>48.8%</td>
</tr>
<tr>
<td>Fatigue</td>
<td>54.7%</td>
<td>14.0%</td>
</tr>
<tr>
<td>Bleeding/hemorrhage*</td>
<td>28.9%</td>
<td>1.1%</td>
</tr>
<tr>
<td>Stomatitis</td>
<td>23.3%</td>
<td>4.3%</td>
</tr>
<tr>
<td>Mucosal inflammation</td>
<td>16.1%</td>
<td>2.9%</td>
</tr>
<tr>
<td>Febrile neutropenia</td>
<td>15.9%</td>
<td>15.9%</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>13.4%</td>
<td>2.9%</td>
</tr>
</tbody>
</table>

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

* Grade 5: 1.3% (ram + doc), 1.3% (plac + doc)

hopeful that as we become more familiar with this promising class of agents, we will be able to manage the associated toxicities, which are rare.

DR LOVE: Would you also discuss the results of the Phase I trial of the anti-PD-1 agent pembrolizumab?

DR GARON: A unique factor affecting this trial is the large focus on biomarker studies. All patients on the Phase I trial needed to undergo a biopsy within 60 days of treatment, and we needed to know whether any staining was present in terms of PD-L1 for most of the cohorts (Garon 2014; [4.2]). In the PD-L1-negative group, the response rate was 9%, which is clearly less than the 23% observed in the PD-L1-positive group. However, the swimmer plot showed that individual patients with PD-L1-negative NSCLC who responded well to therapy seemed to experience the exact same benefits as those with PD-L1-positive disease in the same setting.

It is unclear what the appropriate comparator would be for patients who have received 1 prior treatment, which may have been docetaxel, or for those who have received 2 or more prior treatments. As such, the 9% response rate observed and an ongoing PFS look good. The idea that one should not treat PD-L1-negative disease is difficult to understand because some patients experienced a response.

### 4.2 Results of a Phase I Trial of Pembrolizumab (MK-3475) in Patients with Previously Treated Non-Small Cell Lung Cancer

<table>
<thead>
<tr>
<th></th>
<th>By RECIST v1.1 (ICR)</th>
<th>irRC</th>
<th>All patients</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>PD-L1-positive (n = 159)</td>
<td>PD-L1-negative (n = 35)</td>
<td>PD-L1-positive (n = 177)</td>
</tr>
<tr>
<td>ORR</td>
<td>23%</td>
<td>9%</td>
<td>19%</td>
</tr>
<tr>
<td>DCR</td>
<td>42%</td>
<td>31%</td>
<td>51%</td>
</tr>
<tr>
<td></td>
<td>n = 177</td>
<td>n = 40</td>
<td>n = 177</td>
</tr>
<tr>
<td>Median PFS</td>
<td>11 weeks</td>
<td>10 weeks</td>
<td>16 weeks</td>
</tr>
<tr>
<td></td>
<td>10 mg/kg q2wk (n = 98)</td>
<td>10 mg/kg q3wk (n = 119)</td>
<td></td>
</tr>
<tr>
<td>Select AEs</td>
<td>Any grade</td>
<td>Grade 3-5</td>
<td>Any grade</td>
</tr>
<tr>
<td>Fatigue</td>
<td>24%</td>
<td>1%</td>
<td>16%</td>
</tr>
<tr>
<td>Decreased appetite</td>
<td>10%</td>
<td>0%</td>
<td>8%</td>
</tr>
<tr>
<td>Arthralgia</td>
<td>9%</td>
<td>1%</td>
<td>8%</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>8%</td>
<td>0%</td>
<td>7%</td>
</tr>
<tr>
<td>Nausea</td>
<td>7%</td>
<td>1%</td>
<td>4%</td>
</tr>
</tbody>
</table>

ICR = independent central review; irRC = immune-related response criteria by investigator review; ORR = overall response rate; DCR = disease control rate; PFS = progression-free survival; NR = not reported; AE = adverse event

Garon EB et al. Proc ASCO 2014; Abstract 8020.

**SELECT PUBLICATION**

Rizvi NA et al. Safety and response with nivolumab (anti-PD-1; BMS-936558, ONO-4538) plus erlotinib in patients (pts) with epidermal growth factor receptor mutant (EGFR MT) advanced NSCLC. Proc ASCO 2014; Abstract 8022.
1. An unplanned subset analysis of the results of the Phase III RADIANT trial, which evaluated adjuvant erlotinib versus placebo after complete tumor resection with or without adjuvant chemotherapy for patients with EGFR-positive Stage IB to IIIA NSCLC, demonstrated a statistically significant improvement in __________ with erlotinib therapy for patients with EGFR mutation-positive disease.
   a. Disease-free survival
   b. OS
   c. Both a and b

2. The updated results from the single-arm Phase II SELECT trial of adjuvant erlotinib for patients with resected early-stage EGFR mutation-positive NSCLC demonstrated a 2-year disease-free survival of approximately __________ across multiple disease stages.
   a. 25%
   b. 40%
   c. 90%

3. In a randomized trial of erlotinib with or without bevacizumab as first-line therapy for patients with advanced EGFR-mutant nonsquamous NSCLC, a statistically significant improvement in median PFS was observed with the addition of bevacizumab.
   a. True
   b. False

4. The Lung Cancer Master Protocol is a clinical trial that will assign patients with advanced squamous cell NSCLC based on their genotype to one of several randomized substudies of targeted agents versus standard second-line therapy.
   a. True
   b. False

5. The Phase III SQUIRE trial demonstrated a statistically significant OS benefit with the addition of __________ to gemcitabine/cisplatin as first-line therapy for advanced squamous cell NSCLC.
   a. Ramucirumab
   b. Necitumumab
   c. Afatinib
   d. Crizotinib

6. 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 atezolizumab versus chemotherapy in patients with advanced NSCLC who were positive for the EGFR del(19) mutation.
   a. True
   b. False

7. A Phase I trial of the novel ALK inhibitor X-396 in patients with advanced solid tumors demonstrated partial responses in __________ of patients with ALK-positive tumors.
   a. 90%
   b. 55%
   c. 25%

8. __________ is a second-generation ALK inhibitor recently approved for patients with ALK-positive, metastatic NSCLC that is resistant to or those who are intolerant to crizotinib.
   a. Nivolumab
   b. Ceritinib
   c. Ramucirumab

9. The results of the Phase III REVEL trial of second-line docetaxel with or without ramucirumab for patients with Stage IV NSCLC of both squamous and nonsquamous cell histology after disease progression on a platinum-based regimen demonstrated a statistically significant improvement in __________ with the addition of ramucirumab to docetaxel.
   a. Median OS
   b. Median PFS
   c. Overall response rate
   d. Disease control rate
   e. Both a and c
   f. All of the above

10. The results of the Phase I trial of pembrolizumab (MK-3475) for patients with previously treated NSCLC demonstrated activity in patient groups with __________ in terms of overall response rate and disease control rate.
    a. PD-L1-negative disease
    b. PD-L1-positive disease
    c. Both a and b
EDUCATIONAL ASSESSMENT AND CREDIT FORM

Lung Cancer Update — Issue 2, 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?

<table>
<thead>
<tr>
<th>BEFORE</th>
<th>AFTER</th>
</tr>
</thead>
<tbody>
<tr>
<td>Results of an unplanned subset analysis of patients with EGFR mutation-positive NSCLC treated with adjuvant erlotinib on the RADIANT trial</td>
<td>4 3 2 1</td>
</tr>
<tr>
<td>Responsiveness of patients with PD-L1 receptor-negative disease to the novel anti-PD-1 antibody pembrolizumab</td>
<td>4 3 2 1</td>
</tr>
<tr>
<td>Improvement in OS with the addition of the anti-VEGF receptor monoclonal antibody ramucirumab to docetaxel for patients with locally advanced or metastatic NSCLC on the REVEL study</td>
<td>4 3 2 1</td>
</tr>
<tr>
<td>Pooled analysis of the Phase III LUX-Lung 3 and LUX-Lung 6 trials of afatinib versus chemotherapy in patients with advanced NSCLC harboring — del(19)/L858R — EGFR mutations</td>
<td>4 3 2 1</td>
</tr>
<tr>
<td>Results of an open-label trial of erlotinib with or without bevacizumab as first-line therapy for advanced EGFR mutation-positive nonsquamous NSCLC</td>
<td>4 3 2 1</td>
</tr>
</tbody>
</table>

Practice Setting:
- [ ] Academic center/medical school
- [ ] Community cancer center/hospital
- [ ] Group practice
- [ ] Solo practice
- [ ] Government (e.g., 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:

<table>
<thead>
<tr>
<th>4 = Yes</th>
<th>3 = Will consider</th>
<th>2 = No</th>
<th>1 = Already doing</th>
<th>N/M = LO not met</th>
<th>N/A = Not applicable</th>
</tr>
</thead>
</table>

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
- [ ] Formulate a rational approach for molecular testing of tumors in order to identify potential protocol and off-protocol treatment options for patients. ................................................. 4 3 2 1 N/M N/A
- [ ] Describe mechanisms of tumor resistance to EGFR tyrosine kinase inhibitors, and identify investigational therapeutic opportunities to circumvent this process. .................. 4 3 2 1 N/M N/A
- [ ] Develop an evidence-based approach to the selection of induction and maintenance biologic therapy and/or chemotherapy for patients with advanced non-small cell lung cancer. ............................................................. 4 3 2 1 N/M N/A
- [ ] Recall the scientific rationale for ongoing investigation of novel agents or immunotherapeutic approaches in lung cancer, and counsel appropriately selected patients about study participation. ...................................................................... 4 3 2 1 N/M N/A
EDUCATIONAL ASSESSMENT AND CREDIT FORM (continued)

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

Would you recommend this activity to a colleague?
☐ Yes ☐ No
If no, please explain:

Additional comments about this activity:

As part of our ongoing, continuous quality-improvement effort, we conduct postactivity follow-up surveys to assess the impact of our educational interventions on professional practice. Please indicate your willingness to participate in such a survey.
☐ Yes, I am willing to participate in a follow-up survey.
☐ No, I am not willing to participate in a follow-up survey.

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

<table>
<thead>
<tr>
<th>Faculty</th>
<th>Knowledge of subject matter</th>
<th>Effectiveness as an educator</th>
</tr>
</thead>
<tbody>
<tr>
<td>Joel W Neal, MD, PhD</td>
<td>4 3 2 1</td>
<td>4 3 2 1</td>
</tr>
<tr>
<td>Paul K Paik, MD</td>
<td>4 3 2 1</td>
<td>4 3 2 1</td>
</tr>
<tr>
<td>Leora Horn, MD, MSc</td>
<td>4 3 2 1</td>
<td>4 3 2 1</td>
</tr>
<tr>
<td>Edward B Garon, MD, MS</td>
<td>4 3 2 1</td>
<td>4 3 2 1</td>
</tr>
</tbody>
</table>

Please recommend additional faculty for future activities:

Other comments about the faculty and editor for this activity:

REQUEST FOR CREDIT — Please print clearly

Name: ................................................................. Specialty: ........................................

Professional Designation: ☐ MD ☐ DO ☐ PharmD ☐ NP ☐ RN ☐ PA ☐ Other

Street Address: ................................................................. Box/Suite: ........................................

City, State, Zip: ................................................................. Telephone: ........................................

Fax: ................................................................. Email: .................................................................

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I certify my actual time spent to complete this educational activity to be _________ hour(s).

Signature: ................................................................. Date: .................................................................

The expiration date for this activity is September 2015. To obtain a certificate of completion and receive credit for this activity, please complete the Post-test, fill out the Educational Assessment and Credit Form and fax both to (800) 447-4310, or mail both to Research To Practice, One Biscayne Tower, 2 South Biscayne Boulevard, Suite 3600, Miami, FL 33131. You may also complete the Post-test and Educational Assessment online at www.ResearchToPractice.com/LCU214/CME.
Conversations with Oncology Investigators
Bridging the Gap between Research and Patient Care

Joel W Neal, MD, PhD
Paul K Paik, MD
Leora Horn, MD, MSc
Edward B Garon, MD, MS

FACULTY INTERVIEWS

EDITOR
Neil Love, MD

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