



## INTERVIEW

### Rogerio C Lilenbaum, MD

Dr Lilenbaum is Chief Medical Officer at the Smilow Cancer Hospital and Professor of Medicine at Yale University School of Medicine in New Haven, Connecticut.

## Tracks 1-14

### Lung Cancer Highlights of ASCO 2013

- Track 1** Results of the Phase III RTOG-0617 trial evaluating standard-dose (60 Gy) versus high-dose (74 Gy) conformal chemoradiation therapy with or without cetuximab for Stage III non-small cell lung cancer (NSCLC)
- Track 2** Increased toxicity with high-dose chemoradiation therapy in combination with cetuximab on the RTOG-0617 study
- Track 3** Results of the Phase II IFCT-0801/TASTE trial of customized adjuvant therapy for NSCLC
- Track 4** Investigation of anti-programmed death-1 (PD-1) and programmed death ligand-1 (PD-L1) antibodies
- Track 5** Clinical activity and safety of the PD-L1 antibody MPDL3280A in locally advanced or metastatic NSCLC
- Track 6** BRAF V600E mutations in NSCLC
- Track 7** BRF113928: Interim results of a Phase II study of dabrafenib in BRAF V600E mutation-positive, advanced NSCLC
- Track 8** Results of routine EGFR, HER2, KRAS, BRAF and PI3KCA mutation detection and EML4-ALK gene fusion assessment in 10,000 French patients with NSCLC
- Track 9** Clinical activity of the second-generation ALK inhibitor LDK378 in advanced, ALK-positive NSCLC
- Track 10** Efficacy and safety of crizotinib in patients with advanced ROS1-rearranged NSCLC
- Track 11** Results of PROSE: A Phase III trial of proteomic-stratified (VeriStrat®) second-line erlotinib versus chemotherapy for patients with inoperable, EGFR wild-type or unknown NSCLC
- Track 12** PRONOUNCE: Results of a Phase III study of pemetrexed/carboplatin → maintenance pemetrexed versus paclitaxel/carboplatin/bevacizumab → maintenance bevacizumab for advanced nonsquamous NSCLC
- Track 13** Subset analysis of elderly patients on the PointBreak study: Pemetrexed/carboplatin/bevacizumab → maintenance pemetrexed/bevacizumab versus paclitaxel/carboplatin/bevacizumab → maintenance bevacizumab in Stage IIIB or IV nonsquamous NSCLC
- Track 14** Front-line therapeutic options for pan-wild-type metastatic adenocarcinoma of the lung

## Select Excerpts from the Interview

### Track 1

► **DR LOVE:** What are your thoughts about the Phase III RTOG study reported at ASCO comparing high-dose to standard-dose radiation therapy (RT) with chemotherapy for patients with Stage IIIA/B non-small cell lung cancer (NSCLC)?

► **DR LILENBAUM:** RT at a dose of around 60 Gy is the standard for patients with Stage III NSCLC. Previous Phase II data had suggested that higher doses of RT could be beneficial. The RTOG-0617 study was designed to determine whether high-dose RT (74 Gy) would be superior to standard-dose RT (60 Gy). Patients received RT at 60 Gy or 74 Gy with weekly carboplatin/paclitaxel followed by 2 cycles of consolidation carboplatin/paclitaxel. An evaluation of chemoradiation therapy with or without cetuximab was also part of the study design, but those data were not reported. The results showed that high-dose RT was inferior to standard-dose RT in terms of survival, progression-free survival (PFS) and, perhaps of greatest interest, local recurrence rates (Bradley 2013).

► **DR LOVE:** What dose of RT is being used most frequently in practice, and how will the results of this study affect practice?

► **DR LILENBAUM:** I believe 63 to 66 Gy is the dose most frequently used in practice. I don't believe that the 74-Gy dose is used outside of a clinical trial. However, if oncologists are using this dose, they need to stop immediately because the clear message from this trial was that 60 Gy should be the standard dose for unresectable Stage III NSCLC, irrespective of the chemotherapy regimen.

### Track 3

► **DR LOVE:** Another presentation on local treatment that I'd like your take on was from the TASTE study (Soria 2013). What was reported on that trial?

► **DR LILENBAUM:** TASTE was a customized adjuvant trial in which patients were tested for EGFR mutation and then ERCC1 overexpression. The Phase II feasibility component of that trial was reported at ASCO 2013. The authors reported, much to everybody's surprise, that the ERCC1 assay that they were using was simply not reliable enough for a prospective Phase III trial.

► **DR LOVE:** Even though the assay didn't work, the other interesting aspect of the trial was that the control regimen was cisplatin/pemetrexed, which is being used more now in the United States in the adjuvant setting. This aspect of TASTE was similar to reports from the TREAT trial (Kreuter 2013).

► **DR LILENBAUM:** Yes, this was an important finding. The authors reported that more than 80% of patients were able to complete 4 cycles of treatment with cisplatin/pemetrexed. This was similar to the finding from the TREAT study, which compared cisplatin/pemetrexed to cisplatin/vinorelbine. I believe cisplatin/pemetrexed is emerging as the adjuvant regimen of choice for patients with nonsquamous NSCLC.

### Tracks 4-5

► **DR LOVE:** Another exciting data set from ASCO 2013 evaluated an anti-programmed death ligand-1 (PD-L1) antibody in patients with locally advanced or metastatic NSCLC. Would you talk about that study?

► **DR LILENBAUM:** It is incredibly exciting how immunotherapy is evolving and the difference it is likely to make for patients for whom we had no new therapies. The results with the anti-PD-L1 antibody (MPDL3280A) in NSCLC were dramatic. The overall response rate was 22% for patients with NSCLC, and a response was observed in patients with both nonsquamous and squamous cell histologies. A significant differ-

ence in response rate was reported between those whose tumors were PD-L1-positive versus those whose tumors were not (80% versus 14%) (Spigel 2013; [1.1]). I believe that it would be reasonable to evaluate this agent even in patients whose tumors do not express PD-L1 because of the lack of options for these patients. One of the remarkable features of this agent is that no significant toxicity was observed in this group of patients with heavily pretreated disease.

## 1.1

### Clinical Activity and Safety of the PD-L1 Antibody MPDL3280A in Locally Advanced or Metastatic Non-Small Cell Lung Cancer (NSCLC)

Efficacy*	ORR*	SD ≥24 wk	PFS at 24 wk
NSCLC (n = 41) <sup>†‡</sup>	22%	12%	46%
Nonsquamous (n = 31)	19%	13%	44%
Squamous (n = 9)	33%	11%	44%
Response by PD-L1 status	PD-L1-positive	PD-L1-negative	
NSCLC (n = 41) <sup>†</sup>	80%	14%	
Nonsquamous (n = 31)	67%	14%	
Squamous (n = 9)	100%	17%	

\* Investigator assessed; <sup>†</sup> One patient had undetermined histology status; <sup>‡</sup> Number of prior systemic regimens: 1 (15%), 2 (21%), ≥3 (62%)

ORR = objective response rate; SD = stable disease; PFS = progression-free survival

Spigel DR et al. *Proc ASCO* 2013; **Abstract 8008**.

## Track 9

▶ **DR LOVE:** What are your thoughts on the Phase I trial of the ALK inhibitor LDK378 in advanced, ALK-positive NSCLC?

▶ **DR LILENBAUM:** ALK rearrangements are present in 3% to 7% of patients with NSCLC, and crizotinib is quite active for these patients. However, most patients eventually develop resistance to crizotinib. This is the first clinical trial to demonstrate that LDK378 is active in crizotinib-resistant disease. A response rate of approximately 60% was reported with this agent (Shaw 2013; [1.2]). LDK378 now provides an option other than conventional chemotherapy for these patients. Additionally, in a subset of patients the mechanisms of resistance were identified and LDK378 was also found to be active against tumors with the L1196 mutation. The study also included patients with crizotinib-naïve disease, and LDK378 had excellent activity in that group of patients.

## Track 11

▶ **DR LOVE:** Would you discuss the Phase III study on the predictive value of VeriStrat classification on the survival of patients with advanced NSCLC treated with second-line chemotherapy or erlotinib?

▶ **DR LILENBAUM:** VeriStrat is a serum proteomic signature that can be used to classify patients with NSCLC into VeriStrat good and VeriStrat poor groups based on 8 mass spectral peaks. In the study reported by Lazzari and colleagues, patients with NSCLC had their VeriStrat status determined upon registration and were then randomly

## 1.2

## Phase I Trial of the ALK Inhibitor LDK378 in Advanced, ALK-Positive Non-Small Cell Lung Cancer

	All patients (n = 114)	CRZ pretreated (n = 79)*	CRZ naïve (n = 35) <sup>†</sup>
<b>Overall response rate</b>	58%	57%	60%
Complete response	1%	1%	0%
Partial response	57%	56%	60%
<b>Median progression-free survival</b> (≥400 mg/d) (n = 114)	8.6 mo		

The most common adverse events among all patients were nausea (73%), diarrhea (72%), vomiting (58%) and fatigue (41%).

CRZ = crizotinib; \* 1 response unknown; <sup>†</sup> 4 responses unknown

Shaw AT et al. *Proc ASCO* 2013; **Abstract 8010**.

assigned to either chemotherapy with pemetrexed or docetaxel or to erlotinib. The results indicated that, as expected, the test is prognostic and patients with good VeriStrat status fared much better than those with poor status.

Additionally, the results indicated that the survival of patients with good VeriStrat status (65% to 70% of patients) was similar with chemotherapy and erlotinib. However, patients with poor VeriStrat status had a higher median overall survival with chemotherapy than with erlotinib (Lazzari 2013; [1.3]).

## 1.3

## Results of PROSE: A Prospective Phase III Trial of Proteomic-Stratified (VeriStrat) Second-Line Erlotinib versus Chemotherapy for Patients with Inoperable Non-Small Cell Lung Cancer

Median overall survival	Chemotherapy	Erlotinib	Hazard ratio	p-value
All patients (n = 129, 134)	9.0 mo	7.7 mo	1.14	0.313
VeriStrat good (n = 96, 88)	10.92 mo	10.95 mo	1.06	0.714
VeriStrat poor (n = 38, 41)	6.38 mo	2.98 mo	1.72	0.022

- Overall, patients with VeriStrat good status have better outcomes than those with VeriStrat poor status.
- VeriStrat classification is useful in guiding second-line treatment decision-making for patients with EGFR wild type or unknown EGFR status.

Lazzari C et al. *Proc ASCO* 2013; **Abstract LBA8005**.

 **Tracks 12-13**

► **DR LOVE:** What are your thoughts on the Phase III PRONOUNCE study in advanced nonsquamous cancers (Zinner 2013)?

► **DR LILENBAUM:** In this study, patients were randomly assigned to either carboplatin/pemetrexed with pemetrexed maintenance or the ECOG-E4599 regimen, which is carboplatin/paclitaxel/bevacizumab with bevacizumab maintenance. The primary endpoint was Grade 4 PFS, which means survival free of progression or death but also free of Grade 4 adverse events.

The results indicated no difference in Grade 4 PFS between the 2 regimens. Hematologic toxicity was not that much more favorable for carboplatin/pemetrexed versus carboplatin/paclitaxel/bevacizumab. In fact, anemia and thrombocytopenia were worse on the carboplatin/pemetrexed arm. Neutropenia was worse on the bevacizumab arm, as you would expect. Alopecia and peripheral neuropathy were also more common on the bevacizumab arm.

The data suggest that either regimen can be used, but the small size and unusual endpoint must be considered in comparison to the large data set for the addition of bevacizumab to chemotherapy. I am a little unclear about how a trial like this advances the field.

► **DR LOVE:** Mark Socinski presented a subset analysis of the PointBreak trial at ASCO 2013. Can you also discuss those data?

► **DR LILENBAUM:** PointBreak was a Phase III study comparing 2 regimens — carboplatin/pemetrexed/bevacizumab with maintenance pemetrexed/bevacizumab versus the ECOG-E4599 regimen. The results showed no significant difference between the 2 regimens with respect to overall survival, the primary endpoint (Patel 2012). Both regimens were tolerable, suggesting that either regimen can be used.

At ASCO 2013 Dr Socinski presented the results of a subgroup analysis of elderly patients from the PointBreak trial using age 70 or 75 as a cutoff. No significant difference in overall survival was observed between patients in the different age groups (Socinski 2013).

Based on data from earlier studies, concerns were raised about the use of bevacizumab in elderly patients. This subset analysis indicated that you can administer bevacizumab to elderly patients without significant additional toxicity compared to younger patients. ■

## SELECT PUBLICATIONS

Bradley JD et al. **A randomized phase III comparison of standard-dose (60 Gy) versus high-dose (74 Gy) conformal chemoradiotherapy with or without cetuximab for stage III non-small cell lung cancer: Results on radiation dose in RTOG 0617.** *Proc ASCO* 2013;**Abstract 7501.**

Kreuter M et al. **Randomized phase 2 trial on refinement of early-stage NSCLC adjuvant chemotherapy with cisplatin and pemetrexed versus cisplatin and vinorelbine: The TREAT study.** *Ann Oncol* 2013;24(4):986-92.

Patel J et al. **A randomized, open-label, Phase III, superiority study of pemetrexed (Pem) + carboplatin (Cb) + bevacizumab (Bev) followed by maintenance Pem + Bev versus paclitaxel (Pac) + Cb + Bev followed by maintenance Bev in patients with Stage IIIB or IV non-squamous non-small cell lung cancer (NS-NSCLC).** Chicago Multidisciplinary Symposium in Thoracic Oncology 2012;**Abstract LBPL1.**

Socinski M et al. **A phase III study of pemetrexed (Pem) plus carboplatin (Cb) plus bevacizumab (Bev) followed by maintenance pem plus bev versus paclitaxel (Pac) plus cb plus bev followed by maintenance bev in stage IIIB or IV nonsquamous non-small cell lung cancer (NS-NSCLC): Overall and age group results.** *Proc ASCO* 2013;**Abstract 8004.**

Soria JC et al. **Results of the prospective, randomized, and customized NSCLC adjuvant phase II trial (IFCT-0801, TASTE trial) from the French Collaborative Intergroup.** *Proc ASCO* 2013;**Abstract 7505.**

Spigel DR et al. **Clinical activity, safety, and biomarkers of MPDL3280A, an engineered PD-L1 antibody in patients with locally advanced or metastatic non-small cell lung cancer (NSCLC).** *Proc ASCO* 2013;**Abstract 8008.**

Zinner R et al. **Randomized, open-label, phase III study of pemetrexed plus carboplatin (PemC) followed by maintenance pemetrexed versus paclitaxel (Pac) + carboplatin + bevacizumab (Bev) followed by maintenance bevacizumab in patients with advanced nonsquamous non-small cell lung cancer (NS-NSCLC).** *Proc ASCO* 2013;**Abstract LBA8003.**