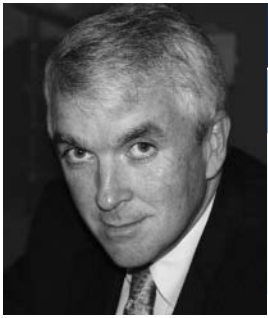

INTERVIEW

Thomas J Lynch Jr, MD

Dr Lynch is Director at Yale Cancer Center, Physician-in-Chief at Smilow Cancer Hospital at Yale-New Haven and Richard and Jonathan Sackler Professor of Internal Medicine at New Haven, Connecticut.

Tracks 1-10

Track 1 EGFR mutation type: Implications for prognosis and response to tyrosine kinase inhibitors (TKIs)

Track 2 Incorporation of the newly FDA-approved irreversible EGFR/HER2 TKI afatinib into the treatment of EGFR-mutant, advanced non-small cell lung cancer (NSCLC)

Track 3 Side effects and toxicity of afatinib alone or in combination with cetuximab

Track 4 Use of afatinib as first-line treatment for EGFR-mutant, advanced NSCLC

Track 5 Continued treatment with erlotinib in patients with slowly progressive, EGFR-mutant NSCLC

Track 6 Ipilimumab in combination with chemotherapy for advanced small cell lung cancer and NSCLC

Track 7 Perspective on immune checkpoint blockade strategies with anti-PD-1 and anti-PD-L1 monoclonal antibodies

Track 8 Targeting BRAF-mutant NSCLC with dabrafenib

Track 9 Next-generation ALK inhibitor LDK378 in crizotinib-naïve and crizotinib-resistant advanced NSCLC

Track 10 Algorithm for molecular testing in nonsquamous NSCLC

Select Excerpts from the Interview

Tracks 1, 10

DR LOVE: What is the current status of research on EGFR and non-small cell lung cancer (NSCLC)?

DR LYNCH: At the large cancer centers, tests using 409-gene panels and whole exome sequencing are used. The questions are, what is evidence based, and what should be done in the community? In the community, I believe all patients with nonsquamous lung cancer should undergo specific testing for EGFR, ALK, ROS, RAF and HER2 expression, and gene panel testing should be performed at diagnosis. For patients with squamous cell NSCLC, it is more difficult to be dogmatic because we don't have specific agents in this setting that would drive treatment decision-making.

DR LOVE: Would you discuss the importance of the presence or absence of EGFR mutations in NSCLC?

DR LYNCH: It is important to know if the disease harbors the exon 19 deletion mutation or exon 21 point mutation. These 2 mutations are the most predictive of benefit from TKIs. Tumors with exon 19 deletions probably respond better, with a longer survival on TKIs. With more testing and sequencing studies, the frequency

of finding T790M increases. A concurrent T790M mutation at diagnosis is crucial because it is a negative prognostic factor that predicts worse outcome.

For patients with disease harboring exon 20 mutations, TKIs show no great evidence of benefit, and that may not be the correct initial treatment even though many anecdotal stories exist of benefit from erlotinib or gefitinib. It is important to review the specific eligibility criteria of the mutation type for trial entry when analyzing outcomes with afatinib, erlotinib or gefitinib. Not all mutations are activating, and not all activating mutations are likely to respond to TKIs.

Tracks 2-3

DR LOVE: How do you think the recently FDA-approved TKI afatinib will be integrated into clinical practice (Sequist 2013)?

DR LYNCH: Afatinib offers great promise in multiple ways. It's an irreversible EGFR inhibitor. In addition, it has activity against HER2. Afatinib offers a degree of benefit similar to that of erlotinib or gefitinib in patients with up-front EGFR mutations, so it's another first-line option. I'm most excited about its combination with cetuximab in TKI-resistant disease. Terrific evidence suggests that cetuximab/afatinib can produce responses in patients with acquired resistance (Janjigian 2012; [1.1]). This will lead to several trials evaluating whether that response improves survival or if it's reasonable to treat with up-front afatinib/cetuximab.

1.1

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

	T790M mutation status		
Clinical outcome	**T790M+** (n = 53)	**T790M-** (n = 39)	**Total** (n = 96)
Confirmed PR	32%	28%	30%
Median DoR	6.4 mo	9 mo	8 mo
Stable disease	49%	36%	45%
Clinical benefit rate	81%	64%	75%
Progressive disease	13%	21%	16%
Not evaluable	6%	15%	9%
Median PFS	NR	NR	4.7 mo
Adverse events (n = 100)	**All grades**	**Grade 1 or 2**	**Grade ≥3**
Rash	97%	79%	18%
Diarrhea	71%	64%	7%
Fatigue	61%	52%	9%
Nausea	53%	50%	3%
Xerosis	52%	49%	3%
Stomatitis	51%	50%	1%
Nail effect	48%	48%	0%

PR = partial response; DoR = duration of response; PFS = progression-free survival; NR = not reported

Janjigian YY et al. *Proc ESMO* 2012;**Abstract 1227O**.

DR LOVE: How would you compare the toxicity profile of afatinib alone or in combination with cetuximab to erlotinib or gefitinib?

DR LYNCH: As a single agent, afatinib causes diarrhea and rash, similar to erlotinib or gefitinib. Slightly more rash or diarrhea may occur with afatinib, although that's not been proven.

In comparison to single-agent afatinib, erlotinib or gefitinib, afatinib/cetuximab is associated with more GI toxicities, diarrhea, rash, paronychia and skin lesions on fingernails and toenails. So the use of afatinib/cetuximab may be a trade-off of toxicity versus improved efficacy.

Track 7

DR LOVE: What is your view on the use of immune checkpoint inhibitors in NSCLC?

DR LYNCH: We have evidence of terrific single-agent activity with anti-PD-1 and anti-PD-L1 antibodies. The major questions are, how do you determine who will respond, what are the biomarkers to predict response, is PD-1 expression the most important predictor of outcome and is anti-PD-L1 antibody as good as anti-PD-1 antibody? At this point we don't know the answers to these questions. It's also too early to know if one has more specificity or toxicity than the other.

I'm excited about combination immunotherapy with ipilimumab and an anti-PD-1 antibody. That's in development and was reported to have activity with an acceptable toxicity profile in melanoma (Wolchok 2013). These agents have the potential to be game changers in early-stage and metastatic disease.

DR LOVE: What is your clinical experience with anti-PD-1 or anti-PD-L1 monotherapy?

DR LYNCH: The single-agent benefits with both agents are remarkable. The side-effect profile is dramatically less than what we see with chemotherapy or TKIs. The prolongation of benefit appears to be longer. ■

SELECT PUBLICATIONS

Lynch TJ et al. **Ipilimumab in combination with paclitaxel and carboplatin as first-line treatment in stage IIIB/IV non-small-cell lung cancer: Results from a randomized, double-blind, multicenter phase II study.** *J Clin Oncol* 2012;30(17):2046-54.

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.

Reck M et al. **Ipilimumab in combination with paclitaxel and carboplatin as first-line therapy in extensive-disease-small-cell lung cancer: Results from a randomized, double-blind, multicenter phase 2 trial.** *Ann Oncol* 2013;24(1):75-83.

Sequist LV et al. **Phase III study of afatinib or cisplatin plus pemetrexed in patients with metastatic lung adenocarcinoma with EGFR mutations.** *J Clin Oncol* 2013;31(27):3327-34.

Wolchok JD et al. **Safety and clinical activity of nivolumab (anti-PD-1, BMS-936558, ONO-4538) in combination with ipilimumab in patients (pts) with advanced melanoma (MEL).** *Proc ASCO* 2013;**Abstract 9012**.

Wozniak AJ et al. **Clinical outcomes (CO) for special populations of patients (pts) with advanced non-small cell lung cancer (NSCLC): Results from ARIES, a bevacizumab (BV) observational cohort study (OCS).** *Proc ASCO* 2010;**Abstract 7618**.