INTERVIEW

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Tracks 1-11

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Select Excerpts from the Interview

Tracks 2-3

DR LOVE: Would you discuss the activity and tolerability of afatinib/cetuximab for patients with NSCLC with acquired resistance to EGFR tyrosine kinase inhibitors (TKIs)?

DR RAMALINGAM: About 60% of patients with NSCLC will develop resistance to EGFR TKIs as a result of the T790M mutation. The remaining 40% will acquire resistance by other mechanisms, such as MET amplification. For patients with the T790M mutation, afatinib/cetuximab has shown the most promising results, with a response rate of approximately 30% (Janjigian 2012; [2.1]). Based on Phase Ib trial results, a Phase III study of afatinib/cetuximab for disease that is resistant to EGFR TKIs has been proposed.

DR LOVE: Would you also discuss what is known about up-front afatinib for patients with advanced NSCLC?

2.1

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

	T790M mutation status		Total*
Best response	**T790M-positive** (n = 53)	**T790M-negative** (n = 39)	(n = 96)
Confirmed PR	32%	28%	30%
CBR	81%	64%	75%

PR = partial response; CBR = clinical benefit rate

* Four patients had NSCLC with EGFR wild type or unknown T790M mutation status.

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

DR RAMALINGAM: In the Phase III LUX-Lung 3 trial, first-line afatinib was superior to cisplatin/pemetrexed in terms of PFS (Yang 2012; [2.2]). For patients with exons 19 and 21 EGFR mutations, the median PFS was about 14 months, which is longer than previously observed with gefitinib or erlotinib (Maemondo 2010; Mok 2009). However, afatinib is associated with a higher incidence of GI toxicities. Although it has not yet been compared head to head to gefitinib or erlotinib, the data with afatinib are suggestive of a greater effect on EGFR-mutated tumors.

2.2

LUX-Lung 3: A Phase III Trial Evaluating Afatinib versus Cisplatin/Pemetrexed (Cis/Pem) as First-Line Therapy for Advanced EGFR-Mutant Non-Small Cell Lung Cancer

Efficacy	**Afatinib** (n = 230)	**Cis/pem** (n = 115)	Hazard ratio	*p*-value
Median PFS: All patients	11.1 mo	6.9 mo	0.58	0.0004
Median PFS: Patients with del(19)/L858R	13.6 mo	6.9 mo	0.47	<0.001
Objective response rate	56.1%	22.6%	—	<0.001
Median duration of response	11.1 mo	5.5 mo	—	—
	Afatinib (n = 229)		**Cis/pem** (n = 111)	
Select adverse events	**All grades**	**Grade 3 or 4**	**All grades**	**Grade 3 or 4**
Diarrhea	95.2%	14.4%	15.3%	0%
Rash/acne	89.1%	16.2%	6.3%	0%
Paronychia	56.8%	11.4%	0%	0%
Stomatitis/mucositis	72.1%	8.7%	15.3%	0.9%
Dry skin	29.3%	0.4%	1.8%	0%
Nausea	17.9%	0.9%	65.8%	3.6%
Decreased appetite	20.5%	3.1%	53.2%	2.7%
Fatigue	17.5%	1.3%	46.8%	12.6%
Vomiting	17.0%	3.1%	42.3%	2.7%
Neutropenia	0.9%	0.4%	31.5%	18.0%
Anemia	3.1%	0.4%	27.9%	6.3%

PFS = progression-free survival

Yang JC et al. *Proc ASCO* 2012;**Abstract LBA7500**.

Track 5

DR LOVE: What is known about the novel irreversible EGFR inhibitor dacomitinib in advanced NSCLC?

DR RAMALINGAM: In a Phase II trial comparing dacomitinib to erlotinib for patients with advanced NSCLC and disease progression on 1 to 2 prior regimens, dacomitinib improved PFS (Ramalingam 2012a). Evaluation of tumor specimens from this trial revealed that patients with KRAS wild-type tumors had about a 2-fold increase in PFS with dacomitinib compared to erlotinib. However, dacomitinib induced a higher incidence of diarrhea and skin toxicities.

In a subset of 30 patients with EGFR-mutant NSCLC, dacomitinib improved PFS compared to erlotinib (Ramalingam 2012b). Although this represents a small number of patients, the data suggest that dacomitinib may be associated with favorable outcomes in EGFR-mutant NSCLC. In support of these data, results of a Phase II trial of up-front dacomitinib demonstrated a PFS of approximately 17 months for patients with EGFR-mutant NSCLC (Janne 2012). This is longer than the PFS observed with erlotinib or gefitinib in Phase III trials. We need more head-to-head comparative studies, however.

The Phase III ARCHER 1009 trial evaluating second- or third-line dacomitinib versus erlotinib in advanced NSCLC (NCT01360554) is ongoing. The primary endpoint is PFS in 2 coprimary populations: all enrolled patients and those with KRAS wild-type NSCLC.

Track 9

DR LOVE: What is your usual first-line therapy and your usual maintenance treatment, if any, for younger patients with metastatic adenocarcinoma of the lung?

DR RAMALINGAM: Our standard approach for such patients has been to use the ECOG regimen of carboplatin/paclitaxel/bevacizumab and continue with bevacizumab maintenance. For patients who have some comorbid illnesses or contraindications to bevacizumab, we often administer pemetrexed-based regimens. What is different now that the PointBreak results have been reported is that we are experiencing some resistance from some of our payers regarding carboplatin/pemetrexed/bevacizumab, so that combination may not be as readily available.

With a younger patient for whom our goal is to achieve a response for improvement of symptoms, we feel more strongly about administering either cisplatin/pemetrexed or the carboplatin/paclitaxel/bevacizumab regimen.

Track 10

DR LOVE: Would you discuss the therapeutic approach of targeting MET in NSCLC?

DR RAMALINGAM: The mechanism of resistance to EGFR TKIs includes the activation of the MET pathway. Targeting MET and EGFR to delay resistance is an attractive strategy. A randomized Phase II study of erlotinib with or without onartuzumab, a monoclonal antibody against the MET receptor, reported no significant difference in

survival in the overall population (Spigel 2011; [2.3]). However, survival was significantly higher with onartuzumab/erlotinib for patients with tumors expressing MET.

A Phase III trial of erlotinib with or without onartuzumab for patients with MET diagnostic-positive NSCLC who have received standard chemotherapy for advanced disease (NCT01456325) is ongoing. Unlike onartuzumab, tivantinib is a MET TKI, which demonstrated favorable outcomes when combined with erlotinib and compared to erlotinib alone in a Phase II trial (Sequist 2011). This study also reported a trend toward PFS and overall survival benefit for patients with nonsquamous cell histology.

The follow-up Phase III study of erlotinib with or without tivantinib for previously treated advanced nonsquamous NSCLC did not select for patients with MET expression (NCT01244191). (Editor's note: This Phase III trial was halted after an interim analysis concluded it would not meet its primary endpoint of improved overall survival.) We await the data to determine if exploratory/post hoc analysis will show a benefit with tivantinib/erlotinib for patients with high MET expression. ■

2.3

OAM4558g: A Phase II Trial of Erlotinib (E) with or without Onartuzumab as Second- or Third-Line Therapy for Advanced Non-Small Cell Lung Cancer

	E + onartuzumab	E + placebo	Hazard ratio	*p*-value
	Patients with positive c-MET immunohistochemistry			
Median progression-free survival	2.9 mo	1.5 mo	0.53	0.04
Median overall survival	12.6 mo	3.8 mo	0.37	0.002
	Patients with negative c-MET immunohistochemistry			
Median progression-free survival	1.4 mo	2.7 mo	1.82	0.05
Median overall survival	8.1 mo	15.3 mo	1.78	0.16
	Intent-to-treat population			
Median progression-free survival	2.2 mo	2.5 mo	1.09	0.69
Median overall survival	8.9 mo	7.4 mo	0.80	0.34

Spigel DR et al. *Proc ASCO* 2011;**Abstract 7505**.

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Mok TS et al. **Randomized, placebo-controlled, phase II study of sequential erlotinib and chemotherapy as first-line treatment for advanced non-small-cell lung cancer.** *J Clin Oncol* 2009;27(30):5080-7.

Ramalingam SS et al. **Randomized Phase II study of dacomitinib (PF-00299804), an irreversible pan–human epidermal growth factor receptor inhibitor, versus erlotinib in patients with advanced non–small-cell lung cancer.** *J Clin Oncol* 2012a;30(27):3337-44.

Ramalingam SS et al. **Dacomitinib (D) versus erlotinib (E) in patients (pt) with EGFR-mutated (mu) advanced non-small cell lung cancer (NSCLC): Analyses from a randomized, Phase 2 Trial.** Multidisciplinary Symposium in Thoracic Oncology 2012b;**Abstract 2**.

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