INTERVIEW

Luis Paz-Ares, MD, PhD

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Tracks 1-8

Select Excerpts from the Interview

Track 1

DR LOVE: Would you comment on the MetLung study evaluating the addition of onartuzumab (MetMAb) to erlotinib for advanced MET-positive NSCLC?

DR PAZ-ARES: The design of the Phase III study was similar to the Phase II study except that it focused on patients with high MET expression (Spigel 2012; [4.1]). In this well-powered study, patients with advanced NSCLC are randomly assigned to erlotinib with or without onartuzumab.

DR LOVE: What is the rationale for combining erlotinib and onartuzumab, and does onartuzumab have a role as a single agent for patients with NSCLC?

DR PAZ-ARES: In tumors that are not dependent on driver mutations it may be important to block 2 or 3 signaling pathways. From 10% to 20% of tumors in patients with mutations may develop a MET amplification as a resistance mechanism after treatment with erlotinib or gefitinib. A similar proportion of patients may experience an autocrine or paracrine increase in hepatocyte growth factor levels, the natural ligand of c-MET. I believe that agents like onartuzumab have a role for EGFR-mutated tumors.

It would be logical to study onartuzumab as a single agent for tumors addicted to MET signaling. Onartuzumab alone could have a role in some forms of lung cancer in which MET mutations arise sporadically.

DR LOVE: What is known about the toxicity of onartuzumab?

DR PAZ-ARES: The Phase II study recorded some cases of edema and mild nausea and vomiting. No significant increase in toxicity was evident in the combination arm with onartuzumab versus the erlotinib-alone arm (Spigel 2011).

4.1

MetLung: A Phase III, Randomized Study of Onartuzumab with Erlotinib versus Placebo with Erlotinib in Advanced, MET-Positive Non-Small Cell Lung Cancer (NSCLC)

Protocol ID: NCT01456325 **Target Accrual:** 480

Eligibility: MET-positive NSCLC; disease progression on 1 to 2 lines platinum-based chemotherapy; patients stratified by MET expression (2+ versus 3+), prior lines of therapy (1 versus 2), EGFR-activating mutation status (yes or no)

Primary endpoint: Overall survival

Spigel DR et al. *Proc ASCO* 2012;**Abstract TPS7616**.

Track 2

DR LOVE: Would you talk about the small-molecule MET inhibitor ARQ 197 (tivantinib) for patients with advanced NSCLC?

DR PAZ-ARES: Tivantinib has demonstrated activity in combination with erlotinib in a randomized Phase II trial (Sequist 2011; [4.2]). A Phase III trial of this agent in NSCLC has recently completed accrual. The level of MET expression was not among the criteria for enrollment, but tissue will be collected for a retrospective analysis of biomarkers.

DR LOVE: Have you observed any toxicity with tivantinib in patients you placed on a trial?

4.2

Phase II Trial of Erlotinib and Tivantinib (ET) versus Erlotinib and Placebo (EP) for Patients with Erlotinib-Naïve, Previously Treated Advanced Non-Small Cell Lung Cancer

Outcome	ET (n = 84)	EP (n = 83)	Hazard ratio	*p*-value
Median PFS (INV)	3.8 mo	2.3 mo	0.81	0.24
Median PFS (IRR)	3.6 mo	2.0 mo	0.74	0.09
Median OS (INV)	8.5 mo	6.9 mo	0.87	0.47

PFS = progression-free survival; INV = investigator assessment; IRR = independent central radiology review; OS = overall survival

Sequist LV et al. *J Clin Oncol* 2011;29(24):3307-15.

DR PAZ-ARES: In general I have not observed a significant increase in toxicity, although some patients had more severe skin toxicity. It is difficult to tell whether patients are receiving erlotinib alone or with tivantinib.

Track 3

DR LOVE: Would you discuss the PARAMOUNT trial and the final results you presented at ASCO 2012?

DR PAZ-ARES: PARAMOUNT is a Phase III study in which patients with NSCLC received 4 cycles of induction therapy with cisplatin and pemetrexed. Patients without disease progression were then randomly assigned to continuation maintenance with pemetrexed or placebo at a ratio of 2 to 1.

At ASCO 2012, we presented the final analysis of overall survival (Paz-Ares 2012; [4.3]). It confirmed the earlier PFS results and the interim analysis of overall survival. The median overall survival from randomization improved from 11 to 14 months. As measured from the time of induction it improved from 14 to 17 months. The hazard ratio was 0.78 whether overall survival was measured from randomization or from the time of induction.

Prior to this trial, no study was adequately powered to demonstrate an increase in overall survival. Now that we have agents with better toxicity profiles, I believe we should maximize the benefit from the drug with continuous maintenance.

4.3

PARAMOUNT: A Phase III Study of Maintenance Pemetrexed (Pem) with Best Supportive Care (BSC) versus Placebo with BSC After Induction with Pem and Cisplatin for Advanced Nonsquamous Non-Small Cell Lung Cancer

	Pem + BSC (n = 359)	Placebo + BSC (n = 180)	Hazard ratio	*p*-value
Median overall survival				
From randomization	13.9 mo	11.0 mo	0.78	0.0195
From induction	16.9 mo	14.0 mo	0.78	0.0191

Median follow-up = 12.5 mo

Paz-Ares L et al. *Proc ASCO* 2012;**Abstract LBA7507**.

Track 5

DR LOVE: Would you comment on the AVAPERL trial evaluating maintenance therapy with pemetrexed and bevacizumab for patients with advanced nonsquamous NSCLC?

DR PAZ-ARES: The AVAPERL trial had an induction phase of 4 cycles of cisplatin/pemetrexed and bevacizumab (Barlesi 2011). Patients who did not experience disease progression after induction were randomly assigned to receive bevacizumab alone or pemetrexed with bevacizumab. PFS from randomization was 7 months versus 3.5 months favoring the combination of pemetrexed and bevacizumab with a hazard ratio of approximately 0.5. When calculated from the time of induction, PFS was 10 months

for maintenance pemetrexed and bevacizumab as compared to about 7 months on the control arm. I believe that these results are encouraging for patients with NSCLC.

DR LOVE: Would you also comment on the PointBreak trial evaluating the "Patel regimen" for advanced NSCLC?

DR PAZ-ARES: The experimental arm of the PointBreak trial is evaluating the Patel regimen of carboplatin/pemetrexed/bevacizumab followed by maintenance pemetrexed/bevacizumab. This treatment is being compared to the conventional ECOG-E4599 regimen of carboplatin/paclitaxel/bevacizumab followed by maintenance therapy with bevacizumab alone. The induction arm and the maintenance arm both include different regimens.

The confounding factor is that if the results are different between the 2 arms, we will not know whether those differences result from differences in the induction or the maintenance phase or both. This study has recently completed accrual, and results should be available soon (Editor's note: Subsequent to this interview the initial results of this study were presented; see figure 4.4). ■

4.4

PointBreak: A Phase III Trial of Pemetrexed (Pem)/Carboplatin (Cb)/Bevacizumab (B) Followed by Maintenance Pem + B versus Paclitaxel (Pac)/Cb/B Followed by Maintenance B for Patients with Advanced Nonsquamous Non-Small Cell Lung Cancer

All patients	Pac/Cb/B (n = 84)	Pem/Cb/B (n = 472)	HR	*p*-value
Median PFS	5.6 mo	6.0 mo	0.83	0.012
Median OS	13.4 mo	12.6 mo	—	1.0
Maintenance patients	(n = 296)	(n = 292)		
Median PFS	6.9 mo	8.6 mo	NR	NR
Median OS	15.7 mo	17.7 mo	NR	NR

PFS = progression-free survival; OS = overall survival; NR = not reported

Patel J et al. Chicago Multidisciplinary Symposium in Thoracic Oncology 2012;**Abstract LBPL1**.

SELECT PUBLICATIONS

Barlesi F et al. **Final efficacy outcomes for patients with advanced nonsquamous nonsmall cell lung cancer randomized to continuation maintenance with bevacizumab or bevacizumab plus pemetrexed after first-line bevacizumab-cisplatin-pemetrexed treatment.** ECCO-ESMO 2011;**Abstract LBA34**.

Paz-Ares L et al. **PARAMOUNT: Final overall survival (OS) results of the phase III study of maintenance pemetrexed (pem) plus best supportive care (BSC) versus placebo (plb) plus BSC immediately following induction treatment with pem plus cisplatin (cis) for advanced nonsquamous (NS) non-small cell lung cancer (NSCLC).** *Proc ASCO* 2012;**Abstract LBA7507**.

Sequist L et al. **Randomized phase II study of erlotinib plus tivantinib versus erlotinib plus placebo in previously treated non-small cell lung cancer.** *J Clin Oncol* 2011;29(24):3307-15.

Spigel DR et al. **The MetLUNG study: A randomized, double-blind, phase III study of onartuzumab (MetMAb) plus erlotinib versus placebo plus erlotinib in patients with advanced, MET-positive non-small cell lung cancer (NSCLC).** *Proc ASCO* 2012;**Abstract TPS7616**.

Spigel DR et al. **Final efficacy results from OAM4558g, a randomized phase II study evaluating MetMAb or placebo in combination with erlotinib in advanced NSCLC.** *Proc ASCO* 2011;**Abstract 7505**.