INTERVIEW

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Track 2 Recent revision to NCCN guidelines regarding crizotinib for ALK-positive non-small cell lung cancer (NSCLC)

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Track 7 Adjuvant treatment for patients with EGFR-mutant NSCLC

Track 8 **Case discussion:** A 76-year-old Chinese man and never smoker with EGFR-mutant, moderately differentiated adenocarcinoma experiences disease progression on erlotinib and is switched to carboplatin/pemetrexed (CP) followed by pemetrexed maintenance

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Track 15 Improved survival for a subset of patients on the randomized Phase II OAM4558g trial evaluating MetMAb in combination with erlotinib for advanced NSCLC

Select Excerpts from the Interview

Track 2

DR LOVE: Would you comment on the recent revision of the NCCN guidelines with respect to crizotinib treatment for ALK-positive non-small cell lung cancer (NSCLC)?

DR NATALE: A few years ago, the guidelines were updated to state that if a patient had EGFR-mutated Stage IIIB/IV lung cancer the preferred first-line treatment was erlotinib. For EGFR wild-type adenocarcinoma, they recommended several different chemotherapies. They also stated that if you administered chemotherapy and subsequently found that the patient had an EGFR mutation, you should add erlotinib. Now they've updated the guidelines to state that if a patient has EML4-ALK-positive disease, the recommended first-line treatment is crizotinib before chemotherapy.

We're making the leap that crizotinib will play out in this setting like EGFR tyrosine kinase inhibitors (TKIs), and I believe it will. The objective response rate with crizotinib in patients with good performance status is 60% or higher (Bang 2010). The data we have are in the second-, third- and fourth-line settings, but the duration of response is 10 to 12 months. We continue to see patients from clinical trials who remain disease free at 2 years and beyond. Some patients fare remarkably well, mirroring what we've seen with EGFR-mutated disease treated with a TKI.

Track 10

DR LOVE: What are your thoughts on induction therapy and maintenance for EGFR wild-type adenocarcinoma?

DR NATALE: The paradigm has evolved to 4 cycles of induction therapy. I believe the preferred regimen is pemetrexed with a platinum agent. For patients with Stage IV disease, carboplatin is completely acceptable — cisplatin is not required — but I would never quibble that one is better than the other.

A randomized European trial is investigating the addition of bevacizumab to cisplatin/pemetrexed, and we will learn whether that results in a survival advantage. Although the AVAiL trial showed a progression-free survival (PFS) advantage, no overall survival (OS) advantage was evident when bevacizumab was added (Reck 2009). No lung cancer trial has proven that maintenance bevacizumab contributes to survival. Still, although we don't have definitive data I believe it could be continued as maintenance after 4 cycles if used as part of induction therapy.

One could also switch to erlotinib maintenance based on the SATURN trial, which reported that patients with EGFR wild-type disease experienced a statistically significant improvement in PFS and OS with maintenance erlotinib (Cappuzzo 2010). The survival advantage was modest, but the hazard ratio (HR) was 0.78, which is close to a 25% relative improvement in survival.

We've also heard preliminary results from the PARAMOUNT study, in which patients received 4 cycles of first-line cisplatin and pemetrexed as induction and were then randomly assigned to observation versus pemetrexed maintenance. The maintenance arm yielded a substantial improvement in PFS, with an HR of 0.6 (Paz-Ares 2011; [1.1]). We expect that to translate to an improvement in OS.

The ATLAS study that randomly assigned patients to maintenance bevacizumab, which was used with induction, alone or combined with erlotinib, did not demonstrate an improvement in survival with the addition of erlotinib to bevacizumab as maintenance therapy, whereas in the SATURN study maintenance with erlotinib demonstrated a modest improvement in survival compared to observation. So, paradoxically, erlotinib and bevacizumab maintenance was not of benefit there. This also mirrors the BeTa study, in which patients in the second-line setting were randomly assigned to erlotinib and placebo or erlotinib and bevacizumab. Although that study showed a PFS advantage, no OS advantage was evident (Herbst 2009).

So the concept of combining an anti-VEGF agent and an EGFR-targeted agent, at least in this population, has failed in 2 randomized clinical trials. For a patient who has received carboplatin/pemetrexed induction, maintenance erlotinib would be a consideration, but I'd be wary of simply adding erlotinib to bevacizumab if induction was with carboplatin/pemetrexed/bevacizumab.

1.1

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

Efficacy — Independent review*	Pem + BSC (n = 316)	Placebo + BSC (n = 156)	Hazard ratio	*p*-value
Median progression-free survival	3.9 mo	2.6 mo	0.64	0.0002

Select Grade 3 or 4 adverse events	Pem (n = 359)	Placebo (n = 180)
Anemia†	4.5%	0.6%
Fatigue†	4.2%	0.6%
Neutropenia†	3.6%	0%
Leukopenia	1.7%	0%

* 88% of patient cases were independently reviewed (472/539)
† Statistically significant between arms ($p \leq 0.05$)

Paz-Ares LG et al. *Proc ASCO* 2011;**Abstract CRA7510**.

Track 12

DR LOVE: Would you discuss BLP25, the MUC1 vaccine currently under investigation?

DR NATALE: Randomized Phase II trials have been conducted with this agent in patients with Stage III disease, and a positive signal was observed (Butts 2011; [1.2]). It showed a potential effect on survival when this vaccine was administered to patients whose tumors expressed the antigen.

A Phase III trial that I participated in enrolled patients with Stage III disease who received chemotherapy and radiation therapy and randomly assigned

them to the vaccine or not after completing treatment (1.3). Presumably these patients had a greatly reduced tumor burden, a situation in which we believe immunotherapy has the best opportunity to affect outcome. ■

1.2

Efficacy of the BLP25 Liposome Vaccine (L-BLP25) in Patients with Stage IIIB or IV Non-Small Cell Lung Cancer

	L-BLP25 + best supportive care (BSC) (n = 88)	BSC alone (n = 83)	Hazard ratio	*p*-value
Median overall survival	17.2 mo	13.0 mo	0.745	NR
Three-year survival rate	31%	17%	—	0.035

Butts C et al. *J Cancer Res Clin Oncol* 2011;137(9):1337-42.

1.3

Multicenter, Phase III, Randomized, Double-Blind, Placebo-Controlled Study of the Cancer Vaccine Stimuvax® (L-BLP25 or BLP25 Liposome Vaccine) in Unresectable Stage III Non-Small Cell Lung Cancer (NSCLC)

Protocol ID: NCT00409188
Target Accrual: 1,514

Eligibility
Unresectable Stage III NSCLC with documented stable disease or objective response after chemoradiation therapy

R

- Single infusion of cyclophosphamide → L-BLP25 qwk x 8 → maintenance L-BLP25
- Single infusion of placebo → placebo qwk x 8 → maintenance placebo

Treatment continues until disease progression.
Primary endpoint: Survival duration

www.clinicaltrials.gov. Accessed December 2011.

SELECT PUBLICATIONS

Bang Y et al. **Clinical activity of the oral ALK inhibitor PF-02341066 in ALK-positive patients with non-small cell lung cancer (NSCLC).** *Proc ASCO* 2010;**Abstract 3**.

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Cappuzzo F et al. **Erlotinib as maintenance treatment in advanced non-small-cell lung cancer: A multicentre, randomised, placebo-controlled phase 3 study.** *Lancet Oncol* 2010;11(6):521-9.

Herbst RS et al. **Biomarker evaluation in the Phase III, placebo (P)-controlled, randomized BeTa trial of bevacizumab (B) and erlotinib (E) for patients (Pts) with advanced non-small cell lung cancer (NSCLC) after failure of standard 1st-line chemotherapy: Correlation with treatment outcomes.** *Proc World Conference on Lung Cancer* 2009;**Abstract B2.1**.

Reck M et al. **Phase III trial of cisplatin plus gemcitabine with either placebo or bevacizumab as first-line therapy for non-squamous non-small cell lung cancer: AVAIL.** *J Clin Oncol* 2009;27:1227-34.