INTERVIEW

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Tracks 1-11

Track 1 Mutations associated with resistance to EGFR TKIs: T790M and c-MET

Track 2 Efficacy and safety of *nab* paclitaxel/carboplatin as first-line therapy for advanced NSCLC

Track 3 BATTLE (Biomarker-integrated Approaches of Targeted Therapy for Lung cancer Elimination) study

Track 4 ZODIAC: A Phase III trial of docetaxel with or without vandetanib as second-line treatment for advanced NSCLC

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Track 8 Lung Cancer Mutation Consortium Protocol: An observational study to determine the frequency of oncogenic mutations in Stage IIIB/IV adenocarcinoma

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Track 11 Inhibition of the phosphatidylinositol 3-kinase pathway as a therapeutic target in NSCLC and other solid tumors

Select Excerpts from the Interview

Track 1

DR LOVE: Would you discuss the development of resistance to EGFR tyrosine kinase inhibitors (TKIs) and the recent development of agents with the potential to overcome this resistance?

DR HERBST: The most exciting aspect of the EGFR TKIs for patients with EGFR-mutant lung cancer is that unprecedented responses are observed with minimal toxicity. However, the median duration of response is probably less than one year because resistance is either present initially or develops quickly. This resistance tends to fall into predefined categories, one of which is due

to a secondary mutation known as T790M, which is another mutation in the EGFR gene. The reason why patients with EGFR mutation in exons 19 and 21 are so sensitive to erlotinib and gefitinib is that these agents can block ATP binding precisely with a high affinity.

However, when the T790M mutation develops, it abrogates that effect, and the irreversible EFGR TKIs, such as BIBW 2992, may be effective in that setting.

A large clinical trial has compared BIBW to placebo for patients with EGFR resistance, which will be an important study and may provide a new agent for the treatment armamentarium (Miller 2010; [3.1]). One might even consider using BIBW 2992 in the up-front treatment setting (Yang 2010; [2.1]).

This is a small population of patients because it's 10 percent of all patients with lung cancer and then a smaller percentage of those who have the specific mutations resulting in resistance to EGFR TKIs. But these are patients for whom we may be able to achieve significant control of their disease without using chemotherapy. So this is a fertile and important area of research.

2.1

LUX-Lung 2: A Phase II Study of BIBW 2992 for Patients with Adenocarcinoma of the Lung and Activating EGFR/HER1 Mutations (N = 129)

Overall response rate	Disease control rate	Median progression-free survival	Median overall survival
67%	86%	14 months	24 months

Comparable efficacy was observed in the first- and second-line settings.

Yang C et al. *Proc ESMO* 2010;**Abstract 367PD**.

Track 2

DR LOVE: Would you comment on the Phase III data with *nab* paclitaxel in advanced NSCLC presented at ASCO 2010?

DR HERBST: This was a large trial with more than 1,000 patients that compared carboplatin and *nab* paclitaxel to the standard carboplatin/paclitaxel combination for the initial management of NSCLC. Paclitaxel is relatively insoluble and therefore has to be mixed with Cremophor. *Nab* paclitaxel uses nanotechnology to deliver paclitaxel and does not require Cremophor. An approach such as this, which has been approved in breast cancer, could potentially be more effective and less toxic because Cremophor causes some serious side effects, such as anaphylaxis.

One facet to keep in mind is that the schedules were somewhat different — *nab* paclitaxel was administered weekly and standard paclitaxel was administered every three weeks. According to an independent review, response rates were higher for the patients who received carboplatin with *nab* paclitaxel than for those who received standard carboplatin/paclitaxel (Socinski 2010; [2.2]).

An interesting observation is that when efficacy is broken down by histologic subtype, the greatest effect was observed in patients with squamous cell carcinoma. I believe that is important because a number of advances in nonsquamous NSCLC, such as pemetrexed and bevacizumab, have been made without any recent advancement in the squamous subtype of NSCLC.

In addition, I believe we need to be aware that in lung cancer, other endpoints, such as PFS and overall survival (OS), are important. The PFS and OS data are currently maturing, and it is understandable that it is taking some time to gather those data, considering that this is an international, multicenter trial.

The toxicity data seemed to favor the *nab* paclitaxel arm, especially in terms of neurotoxicity and some of the other parameters, but we are comparing weekly *nab* paclitaxel to an every three-week paclitaxel regimen. We know that when paclitaxel is administered on a weekly basis, the neurotoxicity can be modulated by the schedule.

We need to keep our eye on the follow-up data because it is desirable for the baseline combination chemotherapy to be as minimally toxic as possible when we are adding a targeted agent to doublet chemotherapy. Certainly carboplatin and *nab* paclitaxel could serve as the backbone regimen in the future, especially for patients with squamous histology.

2.2

Efficacy of Carboplatin/*Nab* Paclitaxel versus Carboplatin/Paclitaxel as First-Line Therapy for Advanced Non-Small Cell Lung Cancer

Objective response by independent review	Carboplatin/ paclitaxel	Carboplatin/ *nab* paclitaxel	Response ratio*	*p*-value
All patients	25% (n = 531)	33% (n = 521)	1.31	0.005
Squamous histology	24% (n = 221)	41% (n = 228)	1.67	<0.001
Nonsquamous histology	25% (n = 310)	26% (n = 292)	—	0.808

* Response ratio > 1 favors *nab* paclitaxel

Socinski MA et al. Presentation. ASCO 2010;**Abstract LBA7511**.

Track 10

DR LOVE: What about maintenance strategies that combine drugs that inhibit EGFR with those that inhibit VEGF, for example, erlotinib and bevacizumab?

DR HERBST: The rationale behind such combinations is attacking both the tumor cells and the microenvironment. The most potent way I have ever approached such a strategy in the clinic is to combine the two approved agents, erlotinib and bevacizumab. The erlotinib/bevacizumab combina-

tion has been taken forward in the ATLAS study as maintenance therapy and has shown an improvement in PFS after completion of an initial platinum-based doublet in combination with bevacizumab (Miller 2009; [2.3]). The SATURN study evaluated single-agent erlotinib for patients who received a platinum-based doublet, and because of a significant improvement in PFS with single-agent erlotinib, the drug just received FDA approval and now can be used in the maintenance setting (Cappuzzo 2010; [2.4]). ■

2.3

ATLAS Phase III Randomized, Double-Blind, Placebo-Controlled Study Evaluating Bevacizumab with or without Erlotinib After Initial Treatment for Advanced Non-Small Cell Lung Cancer

	Bevacizumab + erlotinib (n = 373)	Bevacizumab + placebo (n = 370)	Hazard ratio	*p*-value
Progression-free survival	3.2 months	4.0 months	0.79	<0.0001

Miller VA et al. *Proc ASCO* 2009;**Abstract LBA8002**.

2.4

SATURN Phase III Randomized, Double-Blind, Placebo-Controlled Study Evaluating Erlotinib After First-Line Platinum-Based Doublet Chemotherapy for Advanced Non-Small Cell Lung Cancer

	Erlotinib (n = 437)	Placebo (n = 447)	Hazard ratio	*p*-value
Progression-free survival	12.3 weeks	11.1 weeks	0.71	<0.0001

Cappuzzo F et al. *Lancet Oncol* 2010;11(6):521-9.

SELECT PUBLICATIONS

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.

Miller V et al. **Phase IIb/III double-blind randomized trial of afatinib (BIBW 2992, an irreversible inhibitor of EGFR/HER1 and HER2) + best supportive care (BSC) versus placebo + BSC in patients with NSCLC failing 1-2 lines of chemotherapy and erlotinib or gefitinib (LUX-Lung 1).** *Proc ESMO* 2010;**Abstract LBA1**.

Miller VA et al. **A randomized, double-blind, placebo-controlled, phase IIIb trial (ATLAS) comparing bevacizumab (B) therapy with or without erlotinib (E) after completion of chemotherapy with B for first-line treatment of locally advanced, recurrent, or metastatic non-small cell lung cancer (NSCLC).** *Proc ASCO* 2009;**Abstract LBA8002**.

Socinski MA et al. **Results of a randomized, phase III trial of *nab*-paclitaxel (*nab*-P) and carboplatin (C) compared with Cremophor-based paclitaxel (P) and carboplatin as first-line therapy in advanced non-small cell lung cancer (NSCLC).** *Proc ASCO* 2010;**Abstract LBA7511**.

Yang C et al. **A Phase II study of BIBW 2992 in patients with adenocarcinoma of the lung and activating EGFR/HER1 mutations (LUX-Lung 2).** *Proc ESMO* 2010;**Abstract 367PD**.