INTERVIEW

John Heymach, MD, PhD

Dr Heymach is Associate Professor of Thoracic/Head and Neck Medical Oncology at The University of Texas MD Anderson Cancer Center in Houston, Texas.

Tracks 1-12

Select Excerpts from the Interview

Tracks 3-4

DR LOVE: Would you discuss some of the issues involved in improving the effects of anti-angiogenic drugs for the treatment of NSCLC and other solid tumors?

DR HEYMACH: One initial notion was that angiogenesis inhibitors that were easier to administer, such as the oral TKIs, might be more viable options for long-term dosing, but an issue that wasn't anticipated was that the angiogenesis inhibitors themselves induce changes in the host.

Work from Bob Kerbel's lab in mouse models has shown that angiogenic factors and cytokines induced by TKIs are partly dependent on the tumor and partly dependent on the host.

A publication by this group reported on the use of the VEGF TKI sunitinib in mice in which the investigators had implanted tumors. They reported that pretreatment with the angiogenesis inhibitor accelerated the growth of the tumors (Ebos 2009). This raises the theoretical possibility that the TKI could be ramping up the tumor or accelerating it in some way by increasing host production of angiogenic factors, and when you discontinue the drug that may have a biologic effect.

DR LOVE: Another issue I hear about as I talk with investigators from various areas of expertise is that angiogenesis inhibitors have different efficacies in different tumor types.

DR HEYMACH: That's an extremely important issue, and we can make the initial observation that response rates to single-agent angiogenesis inhibitor therapy are different in different diseases. The best single-agent responses to angiogenesis inhibitors have been observed in renal cell cancer. Renal cell cancer — at least clear cell renal cell cancer — tends to have an angiogenic driver that seems to predominately come from a single pathway, the HIF-1 alpha pathway.

We believe other tumors may have more factors driving angiogenesis — such as the NF-kappa B pathway or inflammatory pathways — but a wider diversity of angiogenic factors is apparent in some of the other disease types. Some tumor types do not respond to anti-angiogenic therapy, and we don't understand why. We don't have the tools to predict which tumors will respond. In pancreatic cancer, no benefit is evident whatsoever with the addition of bevacizumab to chemotherapy. It seems that the tumors can develop bypass pathways to VEGF.

Tracks 5-6, 8-10

DR LOVE: Would you discuss the design of the BATTLE study and the results recently reported at AACR (Kim 2010) and ASCO 2010 (Herbst 2010)?

DR HEYMACH: The BATTLE study randomly assigned more than 300 patients with platinum-refractory disease to one of four arms: erlotinib, erlotinib with the retinoid RXR inhibitor bexarotene, sorafenib or vandetanib. When the study began in 2005 or so, these were the agents that we believed were either standards or had the potential to become standards.

This study is unique and is one of the first of this size and scope to incorporate tumor markers using what we call a Bayesian adaptive randomization design. Every patient underwent a new biopsy, an approach for which oncologists' resistance was the biggest obstacle. After more than 200 biopsies, only one overnight hospitalization occurred, and that patient fared well. This

study demonstrates the feasibility of performing a biomarker-driven, biopsy-requiring study among patients with platinum-refractory lung cancer.

The way the randomization design worked was if the patient had a certain marker profile and experienced a great response to agent number one, then the subsequent randomization favored that marker toward agent number one. It didn't guarantee that the patient would receive agent number one, but it increased the probability.

With time we hope that the drugs become more and more closely associated with the markers that they're more likely to have a response to in real time, so we're learning as we go.

I'd also like to point out that we used a set of what we call primary markers embedded in the study, and the patients were randomly assigned based on these markers. They included obvious factors — EGFR mutations, K-ras mutations and EGFR amplification. Also included were blood-based biomarkers and a rich host of what we call discovery markers. Discovery markers are markers that are not established, but we were evaluating and looking for new predictors of response.

We are still analyzing the data, but initial results were presented at ASCO 2010. Sorafenib appears to have intriguing activity in patients with K-ras mutations (Herbst 2010). We typically think of K-ras mutations as markers of resistance to EGFR inhibitors, and approximately 20 percent of patients with NSCLC harbor K-ras mutations.

DR LOVE: Do you have any theories as to why patients with K-ras-positive tumors would fare better while receiving sorafenib?

DR HEYMACH: K-ras is one of the important pathways downstream of EGFR, but activation of the K-ras pathway is not dependent on EGFR. Constitutive activation of that pathway can occur that essentially bypasses EGFR. Downstream from ras are raf, MEK and ERK. Sorafenib was initially designed and tested as a B-raf inhibitor, and it has some B-raf activity. So you can imagine, if the ras pathway is active, inhibiting downstream of ras at the level of raf or MEK might be an effective strategy.

Another interesting finding related to patients on the vandetanib and erlotinib arms is that patients with high VEGFR2 and VEGF appeared to fare better while receiving vandetanib than the patients who didn't exhibit those markers, whereas high levels of VEGFR2 didn't have the same effects for patients who received erlotinib.

Track 11

DR LOVE: What are your thoughts on the irreversible EGFR TKIs?

DR HEYMACH: Irreversible EGFR inhibitors are potentially an important development in the field. We know that EGFR TKIs, such as gefitinib and erlotinib, bind reversibly to the ATP-binding pocket of the EGFR tyrosine

kinase. The irreversible inhibitors bind to the pocket in a different way, creating an irreversible bond.

We are eagerly awaiting data from a couple of large randomized studies with BIBW 2992, the irreversible EGFR/HER2 TKI. The Phase II data with this agent are impressive, and it may provide another alternative to using reversible EGFR inhibitors. I suspect that BIBW 2992 will become a valuable tool that we'll eventually use in addition to reversible inhibitors. ■

3.1

LUX-Lung 1: A Phase IIb/III Trial of Afatinib (BIBW 2992) with Best Supportive Care (BSC) versus Placebo and BSC for Patients with Non-Small Cell Lung Cancer Failing on Chemotherapy and Erlotinib/Gefitinib

	Afatinib + BSC (n = 390)	Placebo + BSC (n = 195)	Hazard ratio	*p*-value
Efficacy				
Median overall survival	10.78 months	11.96 months	1.08	NS
Median progression-free survival	3.3 months	1.1 months	0.38	<0.0001
Disease control rate at eight weeks	58%	19%	—	<0.0001
Overall response rate	11.0%	0.5%	—	<0.01
Adverse events				
Diarrhea (Grade 3)	87.0%	17.0%	—	—
Rash/acne (Grade 3)	78.0%	14.0%	—	—

Miller V et al. *Proc ESMO* 2010;**Abstract LBA1**.

SELECT PUBLICATIONS

Doebele RC et al. **New strategies to overcome limitations of reversible EGFR tyrosine kinase inhibitor therapy in non-small cell lung cancer.** *Lung Cancer* 2010;69(1):1-12.

Herbst RS et al. **Sorafenib treatment efficacy and KRAS biomarker status in the Biomarker-Integrated Approaches of Targeted Therapy for Lung Cancer Elimination (BATTLE) trial.** *Proc ASCO* 2010;**Abstract 7609**.

Kim ES et al. **The BATTLE trial (Biomarker-integrated Approaches of Targeted Therapy for Lung cancer Elimination): Personalizing therapy for lung cancer.** *Proc AACR* 2010;**Abstract LB-1**.

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**.

Printz C. **BATTLE to personalize lung cancer treatment. Novel clinical trial design and tissue gathering procedures drive biomarker discovery.** *Cancer* 2010;116(14):3307-8.

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**.

Yap TA et al. **Phase I trial of the irreversible EGFR and HER2 kinase inhibitor BIBW 2992 in patients with advanced solid tumors.** *J Clin Oncol* 2010;28(25):3965-72.