



INTERVIEW

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Select Excerpts from the Interview

Track 1

► **DR LOVE:** Would you discuss the current role of cetuximab in NSCLC?

► **DR HERBST:** Over the years there have been several trials of cetuximab for NSCLC in the front- and second-line settings. The FLEX trial evaluated cisplatin/vinorelbine with or without cetuximab in more than 1,000 patients with advanced NSCLC. Although the FLEX trial had a positive overall survival endpoint, the hazard ratio

associated with this benefit was not impressive (Pirker 2011, 2012; [2.1]). So one wonders whether a population of patients exists who might benefit more from cetuximab. If we can identify these patients prospectively, we will be able to administer treatment to only those patients who truly benefit.

In the past decade the Southwest Oncology Group has been involved with studies investigating cetuximab in combination with chemotherapy. We found that patients with the best treatment outcomes in terms of response rate, progression-free survival and overall survival were those with an EGFR gene copy number greater than or equal to 4, as measured by fluorescence in situ hybridization (FISH). A patient with multiple copies of the EGFR gene will make more of the protein. Presumably, those patients are more sensitive to EGFR inhibition with cetuximab.

We conducted some studies, including SWOG-S0342 and SWOG-S0536, which investigated cetuximab with chemotherapy in advanced NSCLC. In both trials, it appeared that patients with an increased EGFR gene copy number had improved outcomes with cetuximab (Hirsch 2008).

► **DR LOVE:** What were the histology criteria for inclusion in these trials?

► **DR HERBST:** The histological subtypes included mixed, squamous cell carcinoma and adenocarcinoma. This is important because it allows for the inclusion of all NSCLC subtypes.

2.1

EGFR Expression as a Predictor of Survival with First-Line Chemotherapy (CT) with Cetuximab (Cet) in Patients with Advanced Non-Small Cell Lung Cancer (NSCLC) on the Phase III FLEX Study

	ITT population		Low EGFR expression		High EGFR expression	
	CT (n = 568)	CT + cet (n = 557)	CT (n = 399)	CT + cet (n = 377)	CT (n = 167)	CT + cet (n = 178)
Median overall survival	10.1 mo	11.3 mo	10.3 mo	9.8 mo	9.6 mo	12.0 mo
	HR = 0.87; p = 0.044		HR = 0.99; p = 0.88		HR = 0.73; p = 0.011	

“High EGFR expression is a tumour biomarker that can predict survival benefit from the addition of cetuximab to first-line chemotherapy in patients with advanced NSCLC. Assessment of EGFR expression could offer a personalised treatment approach in this setting.”

Pirker R et al. *Lancet Oncol* 2012;13(1):33-42.

 **Track 2**

► **DR LOVE:** Would you discuss your ongoing SWOG-S0819 Phase III trial?

► **DR HERBST:** I am the national principal investigator on the SWOG-S0819 trial. It’s designed to evaluate a population of patients who have an increase in the EGFR gene copy number by FISH (2.2). It is an important trial to determine a more specific role for cetuximab in lung cancer. All patients have tissue samples taken at the time of enrollment.

Patients are randomly assigned to carboplatin/paclitaxel or carboplatin/paclitaxel/bevacizumab, with or without cetuximab. The question of the percent of patients with an increased EGFR gene copy number will be investigated prospectively. Patients will

not be stratified based on the EGFR marker. We're making sure that we have the results so that we can look back to see if, in fact, that marker is predictive of outcome.

To make the trial more user friendly and to allow physicians to administer treatment to patients as they would off study, bevacizumab is allowed for those who have not experienced any problems with bleeding and have nonsquamous NSCLC or brain metastases, if treated. The trial will have 4 treatment arms — 2 control arms of carboplatin/paclitaxel or carboplatin/paclitaxel/bevacizumab and 2 experimental arms including cetuximab.

Patients receive a combination of chemotherapy and cetuximab for 6 cycles followed by cetuximab maintenance therapy, which is a bit rigorous. Cetuximab is administered on a weekly basis, which is one of the issues with the drug. Patients who are receiving cetuximab/bevacizumab would receive weekly cetuximab with bevacizumab administration every 3 weeks. Some patients on the control arm will receive no maintenance therapy.

► **DR LOVE:** So far, what have you observed in terms of toxicity?

► **DR HERBST:** Overall, we have not observed any major issues with severe toxicity on any of the treatment arms. It is especially good news that we have not encountered such problems with the patients on the carboplatin/paclitaxel/bevacizumab/cetuximab arm. The most frequently observed side effects are dermatologic, with skin toxicity being the biggest issue with cetuximab.

That being said, based on my own experience and those of other investigators here at Yale and at Vanderbilt, I believe that cetuximab will have a major role in lung cancer, either in combination with chemotherapy as we're testing in the SWOG-S0819 trial

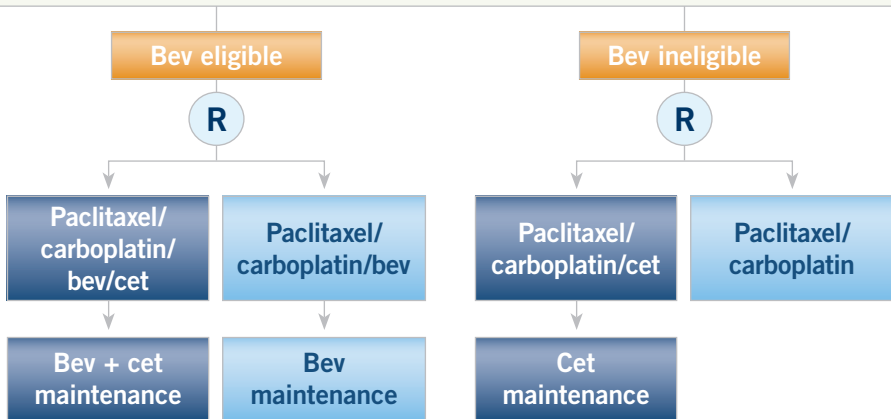
2.2

SWOG-S0819: A Randomized Phase III Trial of Carboplatin/ Paclitaxel with or without Bevacizumab (Bev) and/or Cetuximab (Cet) in Advanced Non-Small Cell Lung Cancer (NSCLC)

Protocol IDs: SWOG-S0819; NCT00946712

Target Accrual: 1,546

Eligibility: Newly diagnosed Stage IV NSCLC or recurrent NSCLC after prior surgery and/or irradiation; histologically/cytologically confirmed adenocarcinoma, large cell, squamous cell carcinomas and unspecified subtypes; no prior chemotherapy for NSCLC; brain metastases controlled for ≥ 2 weeks after treatment; available tumor tissue



or as it was evaluated recently in combination with afatinib (BIBW 2992), the oral irreversible EGFR blocker.

The data evaluating the cetuximab/afatinib combination in patients with NSCLC and acquired resistance to EGFR therapy are compelling. Responses were reported among patients with the T790M mutation and in patients who did not harbor this specific resistance mutation (Janjigian 2011).

I believe we need to continue to closely examine cetuximab in lung cancer. It's a weapon that we shouldn't discard just because of the limited results from the FLEX study.

At the 2011 World Lung Cancer Conference in Amsterdam, I heard a lot of excitement about the use of the H score, which is a quantitative method of determining the intensity of immunostaining over the course of the entire tissue section, to evaluate EGFR expression. High tumor EGFR expression appeared to correlate with better outcome (Pirker 2011, 2012; [2.1]). We've added prospective evaluation of this marker to the SWOG-S0819 trial.

Track 3

► **DR LOVE:** Where do you believe the combination of cetuximab with afatinib fits in the treatment of refractory NSCLC?

► **DR HERBST:** I would say that this combination not only offers an opportunity for patients with refractory NSCLC but would also have a role in the up-front setting. As exciting as it may be to administer EGFR inhibitors to patients harboring EGFR gene mutations, the reality is that all patients will at some point develop resistance. Therefore, it would be great if targeted therapy could be used with the most potent combination from the start, assuming that patients can tolerate the dual skin toxicity.

I believe that investigators will be interested in follow-up clinical trials of the cetuximab/afatinib combination because the data presented at ASCO 2011 are so compelling (Janjigian 2011). It's important to figure out the exact mechanism of action behind this effect. I believe that if we can figure out how the combination works and identify the subgroup of patients who will benefit the most, the combination could be that much more effective. ■

SELECT PUBLICATIONS

Franklin WA et al. **SWOG S0342 and S0536: Expression of EGFR protein and markers of epithelial-mesenchymal transformation (EMT) in cetuximab/chemotherapy-treated non-small cell lung cancer (NSCLC).** *Proc ASCO* 2009;**Abstract 11076.**

Hirsch FR et al. **Increased EGFR gene copy number detected by fluorescent in situ hybridization predicts outcome in non-small-cell lung cancer patients treated with cetuximab and chemotherapy.** *J Clin Oncol* 2008;26(20):3351-7.

Janjigian YY et al. **Activity and tolerability of afatinib (BIBW 2992) and cetuximab in NSCLC patients with acquired resistance to erlotinib or gefitinib.** *Proc ASCO* 2011;**Abstract 7525.**

Pirker R et al. **EGFR expression as a predictor of survival for first-line chemotherapy plus cetuximab in patients with advanced non-small-cell lung cancer: Analysis of data from the phase 3 FLEX study.** *Lancet Oncol* 2012;13(1):33-42.

Pirker R et al. **Epidermal growth factor receptor (EGFR) expression as a predictor of survival for first-line chemotherapy plus cetuximab in FLEX study patients with advanced non-small cell lung cancer (NSCLC).** *Proc IASLC* 2011;**Abstract 1557.**