# Phase II Study of Paclitaxel, Carboplatin, and Cetuximab as First Line Treatment, for Patients with Advanced Non-small Cell Lung Cancer (NSCLC)

## *Results of OPN-017*

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**Background:** Cetuximab has demonstrated synergy with taxanes in preclinical models; as well as single agent activity. We assessed the activity of cetuximab with carboplatin and paclitaxel given on a 4-week schedule, in advanced, chemo-naive non-small cell lung cancer.

**Patients and Methods:** This phase II, single arm, multi-institution study featured standard dosage of cetuximab 400 mg/m$^2$ day 1, then 250 mg/m$^2$ with paclitaxel (100 mg/m$^2$/wk, for 3 weeks), and carboplatin (area under curve = 6) day 1 of each 28 day cycle. After 4 to 6 cycles, in the absence of disease progression or excess toxicity, cetuximab was continued weekly. Primary end point was response rate.

**Results:** Fifty-three patients (median age 63, 51% male) participated. Response rate was 57% (3 complete response and 27 partial response). At a median follow-up of 12.5 months, the estimated overall survival is 13.8 months (95% CI: 9.08–16.02) with an event-free survival rate of 5.53 months (95% CI: 4.77–7.99), 18.9% remain free from progression at 1 year. Improved survival was associated with female gender, absence of prior radiation, PS 0 and epidermal growth factor receptor expression. Toxicities included rash (28% grade 3), nail changes (3.7% grade 3), hypomagnesemia (7.5% grade 3 and 3.7% grade 4), and neutropenia (25% grade 3 and 13% grade 4) in addition to other typical side effects anticipated with paclitaxel/carboplatin. There were no grade 5 toxicities.

**Conclusion:** Combination of cetuximab/paclitaxel/carboplatin in non-small cell lung cancer was well tolerated and clinically active with manageable toxicities. This unique schedule, integrating weekly paclitaxel and cetuximab has not yet been tested in a randomized trial.

**Key Words:** Non-small cell lung cancer, Cetuximab, Immunotherapy, Chemotherapy.

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Monoclonal antibodies are major therapeutic agents in the treatment of malignant disease, and combination antibody and chemotherapy has become a standard approach in the management of many solid and hematologic malignancies.[1,2] Lung cancer is the second most common cancer diagnosed for both genders in the United States, with approximately 213,380 new cases estimated in 2007, and prognosis remains generally poor for patients with advanced disease. The addition of bevacizumab to standard chemotherapy with carboplatin and paclitaxel was shown to improve overall survival of patients with incurable nonsquamous lung cancer in the front-line setting.[3] However, many patients are not appropriate for bevacizumab, including patients with squamous histology, current use of anticoagulation, antecedent hemoptysis, or prior brain metastasis.

Epidermal growth factor receptor (EGFR) is another potential, "exploitable" target for the treatment of non-small cell lung cancer (NSCLC). Patients with NSCLC expressing high levels of ErbB1 have more aggressive disease and an unfavorable prognosis.[4] Studies of single-agent erlotinib in

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incurable NSCLC have shown favorable effects on survival (BR.21) leading to Food and Drug Administration registration in the second and third-line setting.[5] Cetuximab, a humanized, IgG1 mAb, recognizes the EGFR extracellular domain and competes for ligand binding to the receptor, representing an alternative approach to EGFR targeting.[6,7] A recently completed randomized trial of carboplatin and paclitaxel every 3 weeks with cetuximab in patients with advanced lung cancer concluded that the regimen was well-tolerated and active.[8]

There is preclinical evidence for cytotoxic synergy between cetuximab and both platinum and paclitaxel.[9] The study reported here was designed to maximize the therapeutic index[10] and thus employed monthly carboplatin and paclitaxel on days 1, 8, and 15, along with cetuximab weekly. In addition, it was felt that weekly paclitaxel, as opposed to standard dosing at 3-week intervals, would help reduce the incidence of paclitaxel's nonhematologic toxicity, including sensory neuropathy and myalgias/arthralgias.

## PATIENTS AND METHODS

### Study Design

This multicenter, phase II, open label, nonrandomized study in patients with stage IIIB/IV NSCLC was designed to determine the efficacy of first line treatment with a combination regimen of paclitaxel, carboplatin, and cetuximab. Efficacy parameters included response rate (RR), stable disease rate, time to disease progression, overall survival and toxicity. Patients received six 4-week cycles of cytotoxic therapy. Cetuximab was administered at an initial dose of 400 mg/m$^2$ IV day 1 of the first cycle, followed by weekly doses of 250 mg/m$^2$. Paclitaxel 100 mg/m$^2$/wk was administered days 1, 8, and 15 of each 28-day cycle, with carboplatin area under curve = 6 (C-G) added on day 1. The sequence of drug administration was cetuximab, followed by paclitaxel, and then carboplatin. Standard premedications and antiemetics were administered. Patients with CR, partial response (PR), or SD after 4 to 6 cycles of therapy had the option of continuing cetuximab therapy (250 mg/m$^2$/wk) until disease progression, unacceptable toxicity or patient refusal. Patients who could not tolerate chemotherapy due to toxicity could continue on cetuximab monotherapy.

### Toxicity and Response Monitoring

Toxicities related to the study drugs and dose modifications were managed according to the established guidelines for each drug. Worst toxicity grades per patient were tabulated for selected adverse events and laboratory measurements. Adverse events that were serious or resulted in premature and permanent discontinuation of any study drug were described in detail. Adverse events and other symptoms were graded according to the National Cancer Institute, Common Terminology Criteria for Adverse Events, Version 3.0.

Patients were evaluated for response according to Response Evaluation Criteria in Solid Tumors criteria. All patients receiving any treatment were considered evaluable for response, except for patients with the wrong cancer diagnosis. All patients were considered evaluable for safety if they received any treatment. Response confirmation occurred $\geq$4 weeks after criteria for response were met. Patients who completed therapy, in the absence of progression, were followed every 90 days with clinical, laboratory, and radiographic exams until they started new therapy.

### Eligibility Criteria

All patients had histologically or cytologically documented stage IV or IIIB NSCLC (with documented malignant pleural or pericardial effusion) or recurrent NSCLC after either primary surgery or radiation. Patients could not have received any prior systemic chemotherapy for the treatment of NSCLC, including adjuvant chemotherapy. Measurable disease and Eastern Cooperative Oncology Group (ECOG) performance status of 0–1 was required. Patients with asymptomatic brain metastasis were eligible, provided they had completed radiotherapy at least 2 weeks before enrollment and were off corticosteroids. Any radiotherapy must have been completed more than 2 weeks before enrollment, with recovery from all adverse effects. No previous irradiation was allowed to the only area of measurable disease except for unequivocal new lesions that developed in a previously irradiated area. Adequate organ function was defined as absolute neutrophil count $\geq$1500/mm$^3$ and platelets $\geq$100,000/mm$^3$; total bilirubin $\leq$1.5 $\times$ upper limit of normal; aspartate transaminase and alanine aminotransferase $\leq$2.5 $\times$ upper limit of normal; and serum creatinine $\leq$1.5 mg/dl or creatinine clearance $\geq$50 ml/min if serum creatinine was $>$1.5. Patients with tissue available had testing for EGFR expression by immunohistochemistry. All patients signed an institutional review board -approved informed consent for this protocol.

Exclusion criteria included history of prior malignancy, except for adequately treated basal or squamous cell skin cancer, in situ cervical cancer, or other cancer for which the patient had been disease-free for at least 3 years; a significant history of cardiac disease;. uncontrolled seizure disorder; active neurologic disease or symptomatic brain metastasis; prior cetuximab or other therapy that specifically targeted the EGF pathway; known hypersensitivity to Cremophor EL; and grade $>$1 peripheral neuropathy.

### Statistics and Sample Size Determination

This single-arm phase II study recruited 53 patients from Fox Chase Cancer Center and its network partners. The primary end point of this single-stage study was RR for the combined regimen. The planned study size of 50 was determined to distinguish a targeted RR of 35% from the historical control of 20%, based on ECOG 1594.[11] Secondary endpoints included clinical benefit (defined as rate of complete and partial remission [CR and PR] and stable disease [SD]), survival and event-free survival (EFS). Analyses included all treated patients.

Survival was calculated from start of treatment to date of death; EFS was calculated from start of treatment to date of documented disease progression or death in the absence of progression. Survival and EFS outcomes were censored if an end point was not reached or if the patient was lost to follow-up, using date of last follow-up and date of last tumor

 

assessment, respectively. Median and 12-month survival, EFS estimates, and 95%CIs were calculated using the Kaplan-Meier product-limit method. The effects of baseline factors on survival and EFS were examined using the logrank test.

## Assessment and Follow-Up

Baseline history and physical examination including ECOG PS, height, and weight were obtained on all patients. The physical examination was repeated at the start of every chemotherapy cycle. Tumor response was assessed every 8 weeks (Q 2 cycles). All patients who received at least one dose of cetuximab were considered assessable for response. During the trial, and for 4 weeks after the last dose of cetuximab, patients were monitored for adverse events. Biochemistry and hematology laboratory assessments were performed at baseline and on day 1 of each cycle (every 28 days). Weekly CBC was obtained before each dose of chemotherapy. During maintenance therapy with cetuximab, chemistries, including magnesium, and CBC were obtained monthly.

# RESULTS

## Patient Demographics

Table 1 lists patient demographics for this trial. Between March 2005 and May 2006, 53 patients were accrued at FCCC and its Partners affiliates. Fifty-one percent of the patients were male. Median age was 63 years (range, 41–86); 19 patients (36%) were over age 70. Forty-seven percent had ECOG PS-0; 8% had received prior RT, 11% had treated brain metastases, and 96% (51 patients) had stage IV or recurrent disease.

**TABLE 1.** Demographics

| $n = 53$ | Median | Range |
|---|---|---|
| **Age** | **63** | **41–86** |
| | **Number** | **Percent** |
| Age group | | |
| <70 | 34 | 64 |
| >70 | 19 | 36 |
| PS | | |
| 0 | 25 | 47 |
| 1 | 28 | 53 |
| Female | 26 | 49 |
| Male | 27 | 51 |
| Stage | | |
| IIIB | 2 | 3.7 |
| IV | 51 | 96.3 |
| Brain mets | | |
| No | 47 | 89 |
| Yes | 6 | 11 |
| Prior XRT | | |
| Yes[a] | 7 | 13 |
| No | 46 | 87 |
| Race | | |
| White | 45 | 85 |
| AA | 6 | 11 |
| Hispanic | 1 | 2 |
| Asian | 1 | 2 |
| Histology | | |
| Adeno | 33 | 62 |
| Squamous | 6 | 11 |
| BAC | 2 | 4 |
| NOS | 12 | 23 |
| EGFR status | | |
| Unknown | 10 | 19 |
| Negative | 4 | 8 |
| Insufficient | 12 | 23 |
| Positive (NOS)[b] | 5 | 9 |
| +1 | 6 | 11 |
| +2 | 6 | 11 |
| +3 | 10 | 19 |

[a]Five patients with prior whole brain irradiation, 2 with lung or bone radiation.
[b]Positive NOS: Positive EGFR staining but no grading was assigned. BAC, bronchioloalveolar carcinoma.
XRT, radiation; AA, African American, Mets, metastatic disease, PS, performance status.

## Best Response

The overall confirmed RR by intention to treat was 57% (3 CR and 27 PR). Twelve additional patients (23%) had stable disease for an overall disease control rate of 80%. One patient was not evaluable due to brain metastasis at the time of diagnosis (Tables 4 and 5).

## Survival Estimates

With a median follow-up time of 12.5 months, median overall survival for the entire group (Figure 1), based on intention-to-treat analysis, was 13.8 months (95% CI: 9.08–16.02). One and 2 year survival rates were 52.8% (95% CI: 38.6–65.2) and 18.1% (95% CI: 6.4–64.6), respectively. Median EFS was 5.53 months (95% CI: 4.77–7.99) with 18.9% free from progression at 1 year (Figure 2). Of 53 patients on the study, 37 died during the study period and 16 were censored as of the last date of analysis. Five patients remain without disease progression with a median follow-up time of 13.6 months (range, 12.4–16.1 month) as of the time of this writing.

## Overall Survival by Groups

Table 2 summarizes overall survival and EFS data for different patient subgroups. Female patients had better overall survival (median survival 16 months; 95% CI 14.1–20.3) compared with males (median survival 7.6 months; 95% CI 5.7–11, logrank $p = 0.003$). In the subset of patients who had received prior radiation therapy ($n = 7$), the overall survival was 6 months versus 14 months in those who had not received radiation ($p = 0.005$). ECOG PS 1 was also an adverse prognostic indicator; with an overall survival of 7.4 months versus 16 months in PS 0 patients ($p = 0.01$). Event-free survival followed a similar pattern to overall survival: 9.6 months for females versus 5.1 month for males, 3.5 months for patients with prior radiation versus 5.7 months for patients without, 4.6 months for PS 1 patients versus 9.3 months for PS 0. Age, however, had no impact on survival in

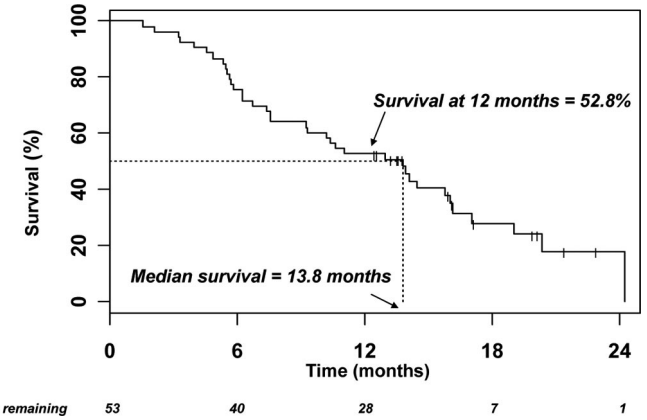


**FIGURE 1.** With a median follow-up time of 12.5 months, median overall survival for the entire group, based on intention-to-treat analysis, was 13.8 months (95% CI: 9.08–16.02). One year survival was 52.8%.

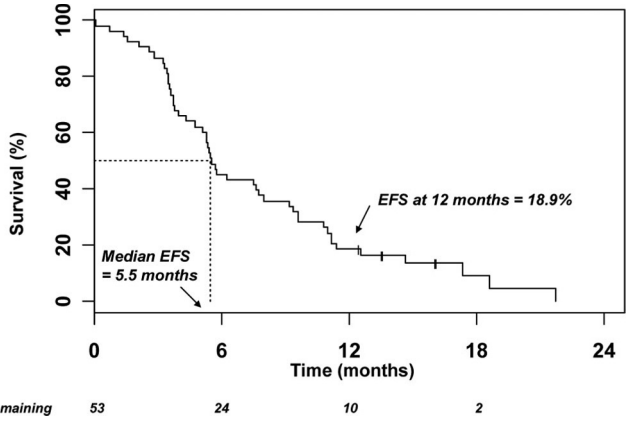


**FIGURE 2.** Median event-free survival (time to disease progression or death in the absence of progression) was 5.53 months (95% CI: 4.77–7.99) with 18.9% free from progression at 1 year.

this analysis. The median survival was similar across all age groups, including 19 patients over the age of 70. Other potential prognostic factors such as weight loss were not routinely determined at baseline.

## Survival and EGFR Status

Table 1, lists the EGFR status of patients involved in this trial. EGFR status was determined by immunohistochemistry, as routinely done by the pathology departments of the participating institutions. Of 31 patients whose EGFR status was known, 4 were negative. With a median follow-up of 12.5 months, patients with any positive EGFR expression had a better median survival (14 months versus 6 months) compared with patients with negative EGFR (Table 2). Median disease- free survival was 6.2 months for any positive EGFR expression versus 3.5 months without EGFR expression.

## Toxicity and Treatment Duration

The median number of chemotherapy cycles administered was four. Twenty patients (38%) received 6 cycles and 34 patients (64%) completed at least four. Of 53 patients on this trial, 15 (28%) went onto maintenance therapy with single agent cetuximab, 1 after 4 cycles and 14 after 6 cycles of chemotherapy. The remainder of patients went off study either due to disease progression before cycle 4 (14 patients, 37%) or due to other causes including toxicity. Median number of maintenance cycles administered was 5; (range, 1–12); each cycle was defined as 4 weekly infusions of cetuximab.

The most common reason for study termination was disease progression (22 patients or 42%). Toxicity was the second most common reason, in 11 patients or 20% (Table 6).

## Toxicities

In general, toxicities were consistent with those anticipated for this regimen (Table 3). The most common attributable grade 3 and 4 toxicities included neutropenia and nail and skin changes. Four patients developed DVTs including 4 reported cases of pulmonary embolism; these were felt to be related to the disease and not the study drugs (Table 3).

Other grade 3 and 4 nonhematologic toxicities included hypomagnesemia (7.5% grade 3; 3.7% grade 4) and fatigue (15% grade 3, no grade 4). Five patients (9%) developed grade 3 sensory neuropathy related to paclitaxel. Grade 1 and 2 dry-cracked skin and nail changes were reported in 21 (40%) and 12 (23%) patients, respectively. These latter skin toxicities were attributed to cetuximab and persisted for the duration of cetuximab administration in most patients. The skin toxicities were managed with Clindamycin gel and Minocyclin.

Overall 20 patients (37.7%) experienced grade 3 or 4 neutropenia (Table 3). Three patients also developed grade 3 thrombocytopenia. Nine patients suffered minor infections with grade 1 and 2 neutropenia, and 20 had infections without neutropenia. These infections were recorded as a result of meticulous follow-up of patients for adverse events. There were no neutropenic fevers with grade 3 or 4 neutropenia. Nor were there any grade 5 toxicities.

## Toxicities During Maintenance Therapy

Predominantly grade 2 toxicities (46% rash, 46% xeroderma/fissures, 54% nail changes, and 31% sensory neuropathy) were observed for the 13 patients who received maintenance therapy. There were no grade 4 and only 2 (15%) grade 3 hypomagnesemias during this phase of treatment. Single-agent cetuximab was generally well tolerated although several patients stopped maintenance treatment because of persistent, distressing skin and nail toxicity.

# DISCUSSION

The primary goals of therapy for patients with Stage IV NSCLC are to increase survival time, palliate symptoms, and improve quality of life. Meta-analyses of trials comparing best supportive care to chemotherapy have shown a survival benefit for chemotherapy along with symptom improvement, weight gain, and improvement in performance status.[12–14] Nevertheless, survival gains have been modest, and toxicity continues to be a problem with most doublet regimens.

 

**TABLE 2.** Survival by Subgroup Analysis

| Subgroups (no) | Median OS (mo) | Logrank *p* | Median EFS (mo) | Logrank *p* | 1 yr OS (%) | 1 yr EFS (%) |
|---|---|---|---|---|---|---|
| Female (26) | 16.1 | 0.003 | 9.6 | 0.0002 | 76.9 | 38.5 |
| Males (27) | 7.6 | | 5.1 | | 29.6 | 0 |
| PS 0 (25) | 16.0 | 0.02 | 9.4 | 0.003 | 72.0 | 32.0 |
| PS 1 (28) | 7.4 | | 4.6 | | 35.7 | 7.1 |
| Prior XRT (7) | 6.3 | 0.003 | 3.5 | 0.002 | 14.3 | 0 |
| No prior XRT (46) | 14.1 | | 5.8 | | 58.7 | 21.7 |
| Age <70 yr (34) | 12.2 | 0.70 | 6.0 | 0.84 | 50.0 | 17.7 |
| Age >70 yr (19) | 14.4 | | 5.4 | | 57.9 | 21.1 |
| EGFR Pos (27) | 14.1 | 0.03 | 6.2 | 0.02 | 63.0 | 18.5 |
| EGFR neg (4) | 6.1 | | 3.5 | | 25.0 | 0.0 |
| Rash (15) | 20.4 | 0.072 | 11.2 | 0.012 | 66.7 | 33.3 |
| No rash (38) | 10.8 | | 5.3 | | 47.4 | 13.2 |

For the EGFR analysis only the samples with known status were included.
For analysis by rash, patients with grade 3 rash were considered as positive versus others.
XRT, radiation therapy; PS, performance status.

**TABLE 3.** Selected Grade 3 and 4 Toxicities

| Toxicity | Grade 3 (percent) | Grade 4 (percent) |
|---|---|---|
| Fatigue | 8 (15.1) | 0 |
| Rash | 15 (28.3) | 0 |
| Nail changes | 2 (3.8) | 0 |
| Pruritus | 2 (3.8) | 0 |
| Vomiting | 3 (5.7) | 0 |
| Diarrhea | 3 (5.7) | 1 (1.9) |
| Sensory neuropathy | 5 (9.4) | 0 |
| Hypomagnesemia | 4 (7.5) | 2 (3.8) |
| Dehydration | 2 (3.8) | 0 |
| DVT | 2 (3.8) | 1 (1.9) |
| Pulmonary embolus | 1 (1.9) | 3 (5.7) |
| HSR | 1 (1.9) | 2 (3.8) |
| WBC | 9 (17.0) | 2 (3.7) |
| ANC | 13 (24.5) | 7 (13.2) |
| HGB | 2 (3.8) | 0 |
| PLT | 3 (5.7) | 0 |

HSR, hypersensitivity reaction; WBC, white blood cells; HGB, hemoglobin; ANC, absolute neutrophil count; PLT, platelets.

**TABLE 4.** Best Response

| Response | Number | Percent |
|---|---|---|
| CR | 3 | 6 |
| PR | 27 | 51 |
| SD | 12 | 22 |
| PD | 2 | 4 |
| NA | 9 | 17 |

**TABLE 5.** Best Response by Gender

| | Female ($n = 26$) | | Male ($n = 27$) | |
|---|---|---|---|---|
| Response | Number | Percent | Number | Percent |
| CR | 2 | 8 | 1 | 4 |
| PR | 14 | 54 | 13 | 48 |
| SD | 5 | 19 | 7 | 26 |
| PD | 1 | 4 | 1 | 4 |
| NA | 4 | 15 | 5 | 19 |

Differences in response by gender were not statistically significant, Fisher exact test $p = 0.94$.
CR, complete response; PR, partial response; SD, stable disease; PD, progression of disease; NA, taken off treatment prior to first assessment due to toxicity or co-morbidity.

**TABLE 6.** Reasons for Treatment Termination

| Reason | Number | Percent |
|---|---|---|
| HSR | 2 | 4 |
| PD | 22 | 42 |
| Dermatologic | 5 | 9 |
| MD choice | 5 | 9 |
| Patient choice | 2 | 4 |
| PS decline | 4 | 8 |
| Intercurrent morbidities[a] | 5 | 9 |
| Toxicities | 8 | 15 |

Toxicities: 3 neurotoxicity, 1 multiple dose reduction, 2 neutropenia, 2 multiple toxicities.
[a]One abscess, 1 MI, 1 ITP, 1 initiation of radiation (in absence of disease progression) and 1 with prolonged hospitalization.
HSR, hypersensitivity reaction; PD, progressive disease; TOX, toxicities; MD, physician decision; PS, deterioration of performance status.

As shown in this report, paclitaxel and cetuximab given on a weekly schedule, combined with carboplatin once a month, yields a well-tolerated and active regimen. Our non-randomized phase 2 trial in a "nonmolecularly selected" patient population surpassed its primary efficacy end point, yielding a median overall survival of 13.8 months, among the highest reported in stage IV disease. It bests any prior efforts of the FCCC or its network.[15,16] Five patients have ongoing responses as of the time of this report with a median follow-up of 13.6 months.

Most of the toxicities in this study were grade 1–2; there were no grade 5 toxicities. Skin and nail toxicities were the most challenging aspect of the management of our patients, in

part because they persisted throughout the course of therapy. Patient tolerance for acute self-limited toxicities may be higher than their tolerance for prolonged lower-grade toxicities of the type observed here. Importantly, patients receiving maintenance cetuximab did not experience significant added toxicities. The number of patients who went on to receive single-agent cetuximab was too small, however, to determine if it improves overall or EFS. The role of maintenance will require phase III testing.

Subgroup analysis suggests that patients who had received prior radiation therapy (whole brain or other regions) had a worse overall and EFS. Reasons for this difference are not immediately apparent, but this observation is hypothesis-generating and suggests that prior RT should be considered a stratification factor in subsequent studies employing this or other C225-combinations. The majority (5) of these previously irradiated patients had received whole brain irradiation. Central nervous system metastasis is an established poor prognostic factor for survival. Female patients fared better compared to males, confirming observations in other studies. Our study also confirms that patients with better performance status (0 versus 1) have improved 1-year overall and EFS (Table 2). The benefits of this therapy were seen across all age groups. Smoking history was not a variable in determining response or survival, as only 3 patients on this study were nonsmokers. Nor was age.

We also showed a correlation between improvement in median survival and EGFR expression. Pooling the data for all patients with any positive EGFR expression, median survival was 14 months in EGFR positive patients versus 6 months for EGFR negative patients ($n = 4$) (logrank $p = 0.02$) The numbers are small, but nonetheless intriguing. They argue for potential patient selection and/or stratification based on tumor EGFR status in future trials with cetuximab.

How do these data compare with similar recently reported studies? In a study of weekly cetuximab plus every 3-week paclitaxel and carboplatin ($n = 31$) an overall disease control rate of 65% (39% stable disease, 26% CR and PR) was reported.[17] All patients with a response had 3+ EGFR tumor expression. With a median follow-up of 19 months, the median time to progression was 5 months, median survival was 11 months, and the 1- and 2-year survival rates were 40% and 16%, respectively. Cetuximab in combination with carboplatin and gemcitabine in chemo-naive patients ($n = 35$) with EGFR positive stage IV NSCLC gave similar results with 10 partial responses (28.6%).[18] Twenty one additional patients had stable disease. The median time to progression was 5.5 months, and the median overall survival was 10.3 months.

In a preliminary report of a completed randomized phase II trial comparing the same 4 week cycle of carboplatin, paclitaxel and cetuximab used in our study with the 3-week cycle of the same regimen[19] the authors reported a disease control (CR + PR + SD) rate of 66% in the 3-week cycle arm versus 62.8% in the 4-week arm. The median overall survival in the 4-week cycle arm was 10.2 months. The results of our effort seem superior to those observed in this randomized phase II study. There is no obvious explanation for the difference; patient selection and tumor EGFR status are key considerations.

Our data suggest an advantage for concurrent cetuximab with a platinating-doublet. Other reports provide a mixed picture. Lynch et al. at World Conference on Lung Cancer in 2007 reported the preliminary results of a phase III trial comparing chemotherapy alone (paclitaxel and carboplatin) to chemotherapy + cetuximab in treatment naive patients, showing an increase in RR, but no significant improvement in PFS[20] based on external radiographic review. Likewise, an ASCO 2007 update of a Southwest Oncology Group study comparing concurrent to sequential cetuximab suggested little difference in outcome.[8] Patient selection could be one reason for the observed difference between our trial and others. Also, the synergism between paclitaxel and cetuximab given on a weekly basis could account for the reported differences. Future larger trials are needed to answer this question. The impetus to explore the role of cetuximab in combination with standard cytotoxic therapy has been further triggered by the statistically significant survival advantage observed in the FLEX trial,[21] for cetuximab in combination with vinorelbine and cisplatin versus chemotherapy alone. This benefit, though modest, was more pronounced in the cohort of non-Asian enrolled on FLEX.

We have shown that a standard platin doublet and cetuximab is well tolerated with preliminary promising efficacy data. The result is noteworthy because to date, small molecule EGFR inhibitors added to standard chemotherapy regimens for NSCLC have not improved overall or progression free survival[22–25] There are some differences in the mechanism of action between antibodies and tyrosine kinase inhibitors that could underlie differential efficacy when combined with chemotherapy. These include (1) interactions with the immune system, Antibody Dependent Cellular Cytotoxicity), (2) the ability of antibodies to clear the cell surface of EGFR, and (3) inhibition of ligand binding to the receptor versus simple inhibition of the receptor tyrosine kinase. To determine if antibodies perform better than tyrosine kinase inhibitors in combination with chemotherapy for the treatment of patients with advanced NSCLC will require results from ongoing and planned randomized phase 2 and 3 studies. The results of our trial provide ample justification for further evaluation of this weekly triplet regimen.

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