Single Arm, Phase II Study of Cisplatin, Docetaxel, and Erlotinib in Patients with Recurrent and/or Metastatic Head and Neck Squamous Cell Carcinomas

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Disclosures of potential conflicts of interest may be found at the end of this article.

TRIAL INFORMATION

- ClinicalTrials.gov Identifier: NCT00076310
- Sponsor(s): Genentech, OSI Pharmaceuticals, and Sanofi Aventis
- Principal Investigator: William Nassib William Jr.
- IRB Approved: Yes

LESSONS LEARNED

- The combination of cisplatin, docetaxel, and erlotinib as frontline treatment for recurrent and/or metastatic head and neck squamous cell carcinomas led to a response rate of 62%.
- This result exceeded the prespecified target response rate of 50% and represented an improvement compared with historical controls.
- This regimen warrants further investigation.

ABSTRACT

Background. The epidermal growth factor receptor (EGFR) plays a key role in the carcinogenesis of head and neck squamous cell carcinomas (HNSCC). We conducted this clinical study to test the hypothesis that the addition of erlotinib to first-line cisplatin and docetaxel for patients with recurrent and/or metastatic HNSCC would yield a response rate of at least 50%, representing an improvement from historical controls.

Methods. Patients with recurrent and/or metastatic HNSCC, with at least one measurable lesion, no prior chemotherapy for recurrent and/or metastatic disease, prior combined modality therapy completed >6 months before enrollment, and performance status ≤2 were treated with cisplatin, docetaxel, and erlotinib for up to six cycles, followed by maintenance erlotinib until disease progression. The primary endpoint was response rate.

Results. Fifty patients were enrolled (42 male, 12 never smokers, 19 with oropharynx cancer). The median number of cycles was five: 31 patients initiated maintenance erlotinib; 14 patients required erlotinib dose reductions. The objective response rate was 62%, and the median progression-free and overall survival were 6.1 and 11.0 months, respectively. Toxicity profiles were consistent with the known side effects of the study drugs.

Conclusion. The study met its primary endpoint and improved response rates compared with historical controls. The findings support further evaluation of the regimen for recurrent and/or metastatic HNSCCs. The Oncologist 2018;23:1–8

DISCUSSION

This single-arm, single-institution, phase II study was designed to test the hypothesis that the addition of erlotinib to first-line cisplatin and docetaxel for patients with recurrent and/or metastatic HNSCC would yield a response rate of at least 50%, representing an improvement over historical controls (the response rate to cisplatin and docetaxel alone observed in a previous trial led by the MD Anderson Cancer Center was 40%). The primary endpoint of the study was met, with an observed objective response rate of 62%. Moreover, the median progression-free survival (6.1 months) and overall survival (11.0 months) achieved by our patient cohort compared favorably with historical controls with chemotherapy alone.

These results are in accordance with a phase I/II clinical trial evaluating the combination of cisplatin and erlotinib in this setting, which showed a response rate of 21%, considered to be
higher than what would be expected with cisplatin alone. Our data add to the growing body of evidence showing that EGFR tyrosine kinase inhibitors have limited activity as monotherapy but may improve outcomes when combined with cytotoxic agents, especially when given in the frontline setting.

In addition to tyrosine kinase inhibitors, EGFR antibodies have also been investigated in phase III trials of recurrent and/or metastatic HNSCC. Currently the combination of platinum, 5-fluorouracil, and cetuximab is considered a standard first-line treatment, given improvements in response rates (20% vs. 36%), median progression-free survival (3.3 vs. 5.6 months), and overall survival (7.4 vs. 10.1 months), when compared with platinum plus 5-fluorouracil alone. The results of our clinical trial are comparable to those obtained with platinum, 5-fluorouracil, and cetuximab. One advantage of the regimen studied herein is the use of a drug that can be administered orally or via feeding tube, obviating the need for weekly infusions, especially in the maintenance setting for patients who achieve longer-term disease control. On the other hand, 40% of our patients experienced diarrhea (10%, grade 3 or 4), which probably resulted from additive toxicities of docetaxel and erlotinib and deserves attention and careful support.

The limited sample size of this trial (with only 19 patients with oropharynx cancer) precludes any conclusions about the efficacy of the regimen in disease that is positive versus negative for human papilloma virus, and this parameter has not been evaluated.

### TRIAL INFORMATION

| Disease                      | Head and neck cancers |
|------------------------------|-----------------------|
| Stage of Disease/Treatment   | Metastatic/advanced   |
| Prior Therapy                | None                  |
| Type of Study - 1            | Phase II              |
| Type of Study - 2            | Single arm            |
| Primary Endpoint             | Overall response rate |
| Secondary Endpoint           | Progression-free survival |

#### Additional Details of Endpoints or Study Design

The overall response rate was the primary endpoint of the study and was determined using RECIST version 1.0. The response status was evaluated after two cycles of treatment and confirmed between 4 and 6 weeks thereafter. A Bayesian design based on predictive probabilities was employed to allow for early stopping if the accumulating evidence suggested treatment ineffectiveness. The maximum calculated sample size was 50 patients, and outcomes were evaluated after the first 15 and 30 patients were treated. If at either interim analysis the predictive probability of a positive study (i.e., posterior probability of response rate >30% at least 90%) was low (<.05), the trial would be stopped. The rule corresponded to stopping the trial if one saw three or fewer responders in 15 patients or 9 or fewer responders in 30 patients. This design provided 92% power with an α of 0.08 to detect a true response rate of 50%.

Eligible patients were required to have histologically or cytologically confirmed metastatic or recurrent head and neck squamous cell carcinoma, with at least one measurable lesion according to RECIST version 1.0; no prior chemotherapy for metastatic or recurrent disease; completed prior combined modality therapy for at least 6 months; Eastern Cooperative Oncology Group (ECOG) performance status ≤2; and normal organ and marrow function, including leukocytes >3,000/μL, absolute neutrophil count >1,500/μL, platelets >100,000/μL, hemoglobin ≥8 g/dL, total bilirubin within normal institutional limits, aspartate aminotransferase/alanine aminotransferase <2.5 × the institutional upper limit of normal (ULN) if alkaline phosphatase is <ULN (alkaline phosphatase may be up to 4 × ULN if transaminases are <ULN), creatinine <2.0 × ULN or creatinine clearance >60 mL/min/1.73 m² for patients with creatinine level above institutional normal. Exclusion criteria included HNSCC of the nasopharynx; history of nonpalliative radiation for metastatic and/or recurrent disease; prior anti-EGFR biologic therapy; brain metastases; pre-existing grade 2 or greater peripheral neuropathy (by the National Cancer Institute Common Terminology Criteria version 2.0); or uncontrolled intercurrent illness.

### Investigator’s Analysis

Active and should be pursued further

### DRUG INFORMATION

| Drug 1             |
|--------------------|
| Generic/Working Name | Cisplatin |
| Drug Type         | Small molecule          |
|------------------|-------------------------|
| Drug Class       | Platinum compound       |
| Dose             | 75 milligrams (mg) per square meter (m²) |
| Route            | IV                      |
| Schedule of Administration | On day 1 every 21 days for a maximum of six cycles |

**Drug 2**

| Generic/Working Name | Docetaxel                |
|----------------------|--------------------------|
| Drug Type            | Small molecule           |
| Drug Class           | Tubulin/microtubules targeting agent |
| Dose                 | 60–75 milligrams (mg) per square meter (m²) |
| Route                | IV                       |
| Schedule of Administration | On day 1 every 21 days for a maximum of six cycles. The first six patients received docetaxel 60 mg/m². Escalation of the docetaxel dose to 75 mg/m² was allowed for patients experiencing minimal toxicity (grade 2) after the first cycle. All subsequent patients were treated with docetaxel 75 mg/m². |

**Drug 3**

| Generic/Working Name | Erlotinib                |
|----------------------|--------------------------|
| Drug Type            | Biological               |
| Drug Class           | EGFR                     |
| Dose                 | 100–150 milligrams (mg) per flat dose |
| Route                | Oral                     |
| Schedule of Administration | Once daily, continuous dosing. The first six patients received erlotinib 100 mg/day. Escalation of the erlotinib dose to 150 mg/day was allowed for patients experiencing minimal toxicity (grade 2) after the first cycle. All subsequent patients were treated with erlotinib 150 mg/day. |

**PATIENT CHARACTERISTICS**

| Number of Patients, Male | 42 |
| Number of Patients, Female | 8  |
| Stage                    | Locoregional recurrence: 31 patients |
|                         | Metastatic disease: 19 patients |
| Age                     | Median (range): 57 |
| Number of Prior Systemic Therapies | 0 |
| Performance Status: ECOG | 0 — 7 |
|                         | 1 — 41 |
|                         | 2 — 2 |
|                         | 3 — Unknown — |

Additional details for Patient and Treatment Characteristics can be found in Tables 1 and 2.

**PRIMARY ASSESSMENT METHOD**

| Title                        | Total Patient Population |
|------------------------------|--------------------------|
| Number of Patients Screened | 50                       |
| Number of Patients Enrolled  | 50                       |
| Number of Patients Evaluable for Toxicity | 50 |
| Number of Patients Evaluated for Efficacy | 50 |
| Evaluation Method            | RECIST version 1.0       |
| Response Assessment CR       | n = 4 (8%)               |
| Response Assessment PR       | n = 27 (54%)             |
| Response Assessment SD       | n = 13 (26%)             |
| Response Assessment PD       | n = 3 (6%)               |
| Response Assessment Other    | n = 3 (6%)               |
| (Median) Duration Assessments PFS | 6.11 months, CI: 5.32–7.59 |
| (Median) Duration Assessments OS | 11.0 months, CI: 8.28–14.9 |
| (Median) Duration Assessments Response Duration | 4.89 months |
This single-arm, single-institution, phase II study was designed to test the hypothesis that the addition of erlotinib to first-line cisplatin and docetaxel for patients with recurrent and/or metastatic head and neck squamous cell carcinoma (HNSCC) would yield a response rate of at least 50%, representing an improvement over historical controls (the response rate to cisplatin and docetaxel alone observed in a previous trial led by the MD Anderson Cancer Center was 40% [1]). The primary endpoint of the study was met, with an observed objective response rate of 62%. Moreover, the median progression-free (6.1 months) (Fig. 1) and overall (11.0 months) (Fig. 2) survival achieved by our patient cohort compared favorably with historical controls with chemotherapy alone [1].
This clinical trial was designed at a time when there was limited evidence of the activity of epidermal growth factor receptor (EGFR)-targeted agents in HNSCCs, especially in regard to tyrosine kinase inhibitors (TKIs) combined with chemotherapy. During the conduct and after completion of this study, evidence arose that EGFR TKIs as single agents had modest activity in HNSCC progressing after platinum-based therapy. Soulieres at al. demonstrated a response rate of 4.3% with single-agent erlotinib [2]. The response rate to single-agent gefitinib at a dose of 500 mg per day was 10.6% [3]. At a lower dose of 250 mg per day, it was 1.4% [4]. Gefitinib was subsequently compared with methotrexate in a phase III study and showed a response rate of 2.7% at 250 mg per day and 7.6% at 500 mg per day but failed to improve survival compared with the chemotherapy arm [5]. Afatinib elicited a response rate of 10% and improved progression-free survival (but not overall survival) over methotrexate in a phase III study [6]. Taken together, these data do not support the use of monotherapy with an EGFR TKI in pretreated HNSCC.

Strategies to improve the efficacy of these drugs included investigations of EGFR TKIs earlier in the course of the disease and/or combinations with cytotoxic agents. Our group [7] and others [8] demonstrated, for example, in separate studies in platinum-naive, early stage, resectable HNSCC, that erlotinib was associated with response rates of 25%–29%, suggesting that the timing of EGFR TKI exposure may influence activity. Indeed, in the current clinical trial, erlotinib was given as first-line therapy for recurrent and/or metastatic disease, in patients with no recent exposure to platinum, and showed improved efficacy compared with historical controls. These results are in accordance with a phase I/II clinical trial evaluating the combination of cisplatin and erlotinib in this setting, which showed a response rate of 21%, considered to be higher than what would be expected with cisplatin alone, although the study did not meet the overly optimistic, prespecified target response rate improvement [9]. In contrast, a phase II study in previously treated patients with recurrent and/or metastatic HNSCC showed no benefit of adding gefitinib to docetaxel in regard to survival or response rates [10], again indicating that the use of EGFR TKIs in later lines of therapy may result in suboptimal outcomes.

In addition to TKIs, EGFR antibodies have also been investigated in phase III trials of recurrent and/or metastatic HNSCC [11–13]. Currently, the combination of platinum, 5-fluorouracil, and cetuximab is considered a standard first-line treatment, given improvements in response rates (20% vs. 36%), median progression-free survival (3.3 vs. 5.6 months) and overall survival (7.4 vs. 10.1 months), when compared with platinum plus 5-fluorouracil alone [12]. The results of our clinical trial are comparable to those obtained with platinum, 5-fluorouracil, and cetuximab. One advantage of the regimen studied herein is the use of a drug that can be administered orally or via feeding tube, obviating the need for weekly infusions, especially in the maintenance setting for patients who achieve longer-term disease control. On the other hand, 40% of our patients experienced diarrhea (10%, grade 3 or 4), which probably resulted from additive toxicities of docetaxel and erlotinib and deserves attention and careful support.

In an attempt to maximize benefit-risk ratios of EGFR inhibitors in HNSCCs, several groups have investigated candidate biomarkers of efficacy. Human papilloma virus (HPV) status was not found to be a predictive marker of benefit from cetuximab added to platinum and 5-fluorouracil in one phase III study [14]. In the randomized trial of platinum, 5-fluorouracil, and panitumumab, the addition of the EGFR antibody was associated with a trend toward improved outcomes primarily in the p16-negative subgroup [13] (although p16 scoring criteria in that study was different than what has been used in pivotal trials in locally advanced disease). Our study only included 19 patients with oropharynx cancers and we did not evaluate HPV/p16 status. However, given the small sample size and non-randomized nature of this study, analysis of efficacy according to HPV status would likely be unable to provide meaningful conclusions. EGFR copy number gain failed as a predictive marker of benefit from cetuximab or gefitinib in the phase III studies [5, 15], indicating that the search for biomarkers in this setting is not straightforward and may require a comprehensive evaluation of multiple pathways, an effort that is currently underway using specimens collected during this study.

In summary, we demonstrated herein that the addition of erlotinib to first-line cisplatin and docetaxel led to improved response rates compared with historical controls. This clinical trial met its primary endpoint, providing support for further investigations of this regimen. Indeed, on the basis of these findings, we launched and completed a randomized, double-blind, placebo-controlled phase II study of platinum and docetaxel with or without erlotinib. Results recently presented in abstract form confirmed the superiority of the erlotinib-containing arm [16]. Taken together, the data from the described single-arm phase II trial and the randomized phase II trials provide a strong rationale for the use of platinum, docetaxel, and erlotinib as frontline therapy for recurrent and/or metastatic HNSCCs.

**ACKNOWLEDGMENTS**

This work was supported by NIH grant P30 CA016672, Cancer Prevention Research Institute of Texas grant RP140464, and a grant from the Conquer Cancer Foundation.

**DISCLOSURES**

William N. William Jr.: Roche/Genentech (C/A), Astellas Pharmaceuticals, Eli Lilly, Bristol-Meyers Squibb, Merck, Astellas Pharmaceuticals, Boehringer Ingelheim Pharmaceuticals (RF), AstraZeneca, Roche, Genentech (H); Anne S. Tsao: Boehringer-Ingelheim Pharmaceuticals, Bristol-Myers Squibb, Genentech, Eli Lilly, Merck (RF). The other authors indicated no financial relationships.

(C/A) Consulting/advisory relationship; (RF) Research funding; (E) Employment; (ET) Expert testimony; (H) Honoraria received; (OI) Ownership interests; (IP) Intellectual property rights/inventor/patent holder; (SAI) Scientific advisory board

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FIGURES AND TABLES

Table 1. Patient characteristics

| Characteristic                  | Number of patients, n (%) |
|--------------------------------|---------------------------|
| Age, years, median (range)     | 57 (39–72)                |
| Sex                            |                           |
| Male                           | 42 (84)                   |
| Female                         | 8 (16)                    |
| Performance status             |                           |
| 0                              | 7 (14)                    |
| 1                              | 41 (82)                   |
| 2                              | 2 (4)                     |
| Disease status at entry        |                           |
| Locoregional recurrence        | 31 (62)                   |
| Metastatic disease             | 19 (38)                   |
| Prior treatment                |                           |
| Radiotherapy alone             | 4 (8)                     |
| Surgery + radiotherapy         | 20 (40)                   |
| Chemotherapy + radiotherapy    | 5 (10)                    |
| Chemotherapy + radiotherapy +  |                           |
| surgery                        | 14 (28)                   |
| Untreated                      | 7 (14)                    |
| Smoking status                 |                           |
| Current                        | 13 (26)                   |
| Former                         | 25 (50)                   |
| Never                          | 12 (24)                   |
| Primary site                   |                           |
| Oropharynx                     | 19 (38)                   |
| Oral cavity                    | 15 (30)                   |
| Larynx                         | 11 (22)                   |
| Hypopharynx                    | 3 (6)                     |
| Unknown primary site           | 2 (4)                     |

Table 2. Treatment characteristics

| Characteristic                  | Metric          |
|--------------------------------|-----------------|
| Median number of cycles        |                 |
| Cisplatin                      | 5               |
| Docetaxel                      | 5               |
| Erlotinib                      | 5               |
| Initiated maintenance erlotinib, n |                |
| No                             | 19              |
| Yes                            | 31              |
| Median duration of maintenance erlotinib, weeks | 17 |
| Median dose intensity, mg/m²   |                 |
| Cisplatin                      | 75              |
| Docetaxel                      | 75              |
| Erlotinib dose reductions, n   |                 |
| No                             | 36              |
| Yes                            | 14              |

Figure 1. Progression-free survival (bold line) and 95% confidence interval (dotted lines).

Figure 2. Overall survival (bold line) and 95% confidence interval (dotted lines).

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