Weekly Docetaxel, Cisplatin, and Cetuximab in Palliative Treatment of Patients with Squamous Cell Carcinoma of the Head and Neck

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 Trial Information

- ClinicalTrials.gov Identifier: NCT01437449
- Sponsor(s): None
- Principal Investigator: A. Dimitrios Colevas
- IRB Approved: Yes

 Lessons Learned

- Chemotherapy for recurrent, metastatic squamous cell carcinoma of the head and neck need not be known for extreme toxicity.
- The weekly regimen studied here has been demonstrated to be tolerable and effective.

 Abstract

 Background. The objective of this study was to establish the response rate, progression-free survival (PFS) and overall survival (OS), and safety profile of weekly docetaxel, platinum, and cetuximab (TPC) in patients with relapsed or metastatic squamous cell carcinoma of the head and neck (SCCHN).

 Materials and Methods. Twenty-nine patients with metastatic or recurrent SCCHN with an Eastern Cooperative Oncology Group (ECOG) performance status <3 were enrolled in an institutional review board-approved phase II trial. This study permitted prior chemoradiation, radiation, and/or surgery, provided that 3 months had elapsed since the end of the potentially curative treatment. Patients received cisplatin 30 mg/m² or carboplatin area under the curve (AUC) 2, docetaxel 30 mg/m², and cetuximab 250 mg/m² weekly for 3 weeks, followed by a break during the fourth week, for a 28-day cycle. Planned intrapatient dose modifications were based on individual toxicity.

 Results. Twenty-seven patients received TPC and were evaluable for response and toxicity. Rates of complete response (CR), partial response (PR), and confirmed PR were 3%, 52%, and 30%, respectively. The overall objective response rate was 56%. Estimated median PFS and OS were 4.8 and 14.7 months, respectively. The rates of grade 3 and 4 worst-grade adverse events (AEs) per patient were 85% and 7%, respectively. Dose density through cycle 4 was preserved for all patients; however, treatment beyond cycle 6 with the TPC regimen proved unfeasible.

 Conclusion. Weekly docetaxel, cisplatin, and cetuximab is an effective regimen for patients with metastatic or recurrent SCCHN. Response rates, PFS, and OS compare favorably with other combination chemotherapy treatments. Grade 4 toxicity rates observed in this study were substantially lower than those described with regimens using less frequent, higher-dose chemotherapy schedules. The Oncologist 2018;23:764–e86

 Discussion

The motivation behind this project was our observation that the so-called EXTREME regimen, which is considered the standard of care by many for these patients, is appropriately named for its extreme toxicity and inconvenience. Our hypothesis was that the exchange of a taxane for infusional fluorouracil (5-FU) and a more frequent, lower-dose schedule in a regimen we have named “TPC” would preserve...
Table 1. Tumor response rates to docetaxel, platinum, and cetuximab

| Best response | n (%) |
|---------------|-------|
| CR            | 1 (3) |
| PR, total     | 14 (52)|
| PR, confirmed | 8 (30) |
| PR, unconfirmed| 6 (22) |
| SD            | 5 (19) |
| PD            | 6 (22) |
| No data       | 1 (4)  |
| Objective response (CR + PR + unconfirmed PR) | 15 (56) |

Abbreviations: CR, complete response; PD, progressive disease; PR, partial response; SD, stable disease.

**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   | Toxicity              |
| Secondary Endpoint   | Complete response rate|
| Secondary Endpoint   | Progression-free survival |
| Secondary Endpoint   | Tolerability          |
| Secondary Endpoint   | Deliverability        |
| Secondary Endpoint   | Safety                |

**Additional Details of Endpoints or Study Design**

**Materials and Methods**

Patients with histologically proven SCCHN whose cancers were not amenable to treatment with surgical resection or radiotherapy with curative intent were enrolled on a Stanford University review board-approved, phase II study of TPC. Informed consent was obtained prior to initiation of therapy. Eligibility was restricted to patients with an ECOG performance status of 0–2 with measurable disease and peripheral neuropathy grade < 2. Adequate organ function was required as follows: absolute neutrophil count > 1,500/mm³, platelets > 100,000/mm³, aspartate aminotransferase and alanine aminotransferase < 2.5 × upper limit of normal (ULN; except when liver metastases were documented, in which case up to 5 × ULN was allowed), total bilirubin < 1.5 × ULN (except if the patient had Gilbert’s syndrome, in which case up to 2.5 × ULN was allowed), and serum creatinine < 1.5 mg/dL or an estimated creatinine clearance from 24-hour urine collection > 50 mL/minute. Patients must not have received prior palliative chemotherapy. Patients who were treated with chemoradiation, radiation, and/or surgery as part of a curative plan were eligible, but this treatment must have been completed 3 months prior to enrollment. Criteria for exclusion were pregnancy, breast feeding, active infection, and prior grade 3 allergic or infusion reactions to docetaxel, cisplatin, or cetuximab. Patients with other malignancies treated curatively more than 1 year prior to enrollment without evidence of relapse at time of enrollment were eligible. Patients with brain metastasis were eligible only if there was no evidence of central nervous system (CNS) progression by CNS imaging at least 30 days after definitive CNS treatment (resection or radiation).

**Treatment Regimen**

A loading dose of 400 mg/m² cetuximab was given intravenously for cycle one. Docetaxel 30 mg/m² and cisplatin 30 mg/m² (TP) and cetuximab 250 mg/m² were then administered intravenously every week on days 1, 8, and 15, followed by a break during the fourth week of each 28-day cycle, for all subsequent doses. Carboplatin AUC 2 was substituted for cisplatin for renal or hearing impairment at baseline or during study treatment. If the loading dose of cetuximab was given more than 5 days before the first scheduled triplet dose, then cycle 1 included the loading dose and the three doses of triplet (TPC) therapy. If the loading dose of cetuximab was given less than 5 days before the first scheduled TP dose, then cycle 1, week 1, included the loading dose and TP only. If a dose of cetuximab was held during weeks 1–3, the dose was given during the fourth week. All confirmed complete responders were treated with TPC for an additional two cycles beyond confirmation of CR. Cetuximab was continued until disease progression.

Dose reductions for agent-associated high-grade (generally grade 3 or higher) toxicities were incorporated as follows. The suspected agent was held for up to 2 weeks, then restarted at a lower dose while other agents were continued at the same dose. Any patients with AEs that had not resolved to grade 1 within 2 weeks were discontinued from study treatment for that particular agent. Dose reduction levels for docetaxel and cisplatin were 25 mg/m² and 20 mg/m². Carboplatin was substituted for cisplatin for neuropathy, hearing loss, or renal dysfunction. For patients with grade 4 acneiform rash toxicity, cetuximab was held for two doses. For the first occurrence of rash, if there was improvement, there was no dose change upon cetuximab resumption. For each subsequent occurrence, if there was improvement, cetuximab was reduced to 200 mg/m² and 150 mg/m². activity while substantially reducing both toxicity and inconvenience. We believe the results of this trial provide preliminary confirmation of this hypothesis. The response rates we observed were numerically superior to two prior benchmark studies, and grade 4 AEs were markedly lower than seen in these same benchmark studies.

Although the field is evolving with the development of immunotherapies and targeted therapies, we assert that regimens such as TPC could be considered instead of the EXTREME regimens in future development of definitive trials likely to involve combinations of immunotherapy and chemotherapy in this patient population [1–8].

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If there was no improvement, cetuximab was discontinued. There was no dose reduction below dose level minus two for any agent. No dose re-escalations were permitted. If patients experienced a mild or moderate (grade 1 or 2) infusion reaction with cetuximab, the infusion rate was permanently reduced by 50%. Cetuximab was permanently discontinued in patients who experienced severe (grade 3 or 4) infusion reactions.

**Response and Toxicity Criteria**

Patients were formally evaluated for treatment-related adverse events from the time of their first dose of TPC. This included lab value analysis (blood counts and serum chemistries) and clinical evaluation prior to every systemic therapy dose, which occurred 3 out of every 4 weeks while patients were on combination treatment and weekly without break during their cetuximab-only treatment times. Toxicities were graded according to the Common Terminology Criteria for Adverse Events, version 4.0 [9]. Toxicities were followed until resolution. Tumor response and progression was evaluated using the Response Evaluation Criteria in Solid Tumors (RECIST) guideline, version 1.1 [10] Patients were assessed for response every 8 weeks ± 1 week. The best overall response was the best response recorded from the start of treatment until disease progression or recurrence, taking as reference for progressive disease the smallest measurements recorded since the treatment started.

**Statistical Considerations**

The primary objective of the trial was to determine the overall response rate to TPC. A two-stage Simon design was used with an α error type of 0.1 and β type error of 0.1 [11]. Because there were at least three responses seen in the first 10 patients, additional patients were enrolled until 27 patients who were evaluable for response were treated. Patients must have received at least one cycle of weekly TPC in order to be evaluable for response. Using these criteria, we posited that 10 or more responders would be the benchmark by which we would declare this regimen to be of further interest. Secondary endpoints included achieved dose intensity, PFS, OS, and toxicity. OS and PFS were defined as the interval from first chemotherapy treatment to death or progression of disease, respectively. Kaplan-Meier survival estimates were used for evaluating PFS and OS with pointwise 95% confidence intervals (CIs) calculated on log (survival). Median survival estimates were obtained from the Kaplan-Meier estimates, as were 95% confidence intervals for median survival equal to the range of survival times for which the confidence intervals contained 0.5.

**Investigator’s Analysis**

Active and should be pursued further

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**Drug Information**

| Drug | Generic/Working Name | Drug Type | Drug Class | Dose | Route |
|------|----------------------|-----------|------------|------|-------|
| Drug 1 | Cisplatin | Small molecule | Platinum compound | 30 milligrams (mg) per square meter (m²) | IV |
| Drug 2 | Carboplatin | Small molecule | Platinum compound | AUC 2 | IV |
| Drug 3 | Docetaxel | Small molecule | Microtubule-targeting agent | 30 milligrams (mg) per squared meter (m²) | IV |
| Drug 4 | Cetuximab | Antibody | Anti epidermal growth factor receptor (EGFR) | 250 milligrams (mg) per square meter (m²) | IV |

**Patient Characteristics**

| Number of Patients, Male | Number of Patients, Female |
|--------------------------|---------------------------|
| 23                       | 4                         |
Stage: All patients with incurable metastatic or recurrent squamous cell carcinoma of the head and neck. Patients who were treated with chemoradiation, radiation, and/or surgery as part of a curative plan were eligible, but this treatment must have been completed 3 months prior to enrollment.

Age: Median (range): 60 (24–80) years

Number of Prior Systemic Therapies: 0

Other: Prior therapy clarification: surgery, 14 patients; radiation, 21 patients; chemotherapy (as part of attempted curative chemoradiation plan). Prior agents: docetaxel, 6 patients; cisplatin, 16 patients; 5-FU, 4 patients; cetuximab, 6 patients; bevacizumab, 1 patient.

**PRIMARY ASSESSMENT METHOD**

| Title                                      | Total Patient Population |
|--------------------------------------------|--------------------------|
| Number of Patients Screened                | 29                       |
| Number of Patients Enrolled                | 29                       |
| Number of Patients Evaluable for Toxicity  | 27                       |
| Number of Patients Evaluated for Efficacy  | 27                       |
| Evaluation Method                          | RECIST, version 1.0      |
| Response Assessment CR                     | n = 1 (3%)               |
| Response Assessment PR                     | n = 14 (52%)             |
| Response Assessment SD                     | n = 5 (19%)              |
| Response Assessment PD                     | n = 6 (22%)              |
| Response Assessment OTHER                  | n = 1 (4%)               |
| (Median) Duration Assessments PFS          | 4.8 months, CI: 2.7–6.6  |
| (Median) Duration Assessments OS           | 14.7 months, CI: 8.3–    |

Kaplan-Meier Time Units, months

| Time of scheduled assessment and/or time of event | No. progressed (or deaths) | No. censored | Percent at start of evaluation period | Kaplan-Meier % | No. at next evaluation/No. at risk |
|--------------------------------------------------|-----------------------------|--------------|--------------------------------------|----------------|------------------------------------|
| 03                                               | 01                          | 1            | 100.00                               | 96.15          | 25                                 |
| 06                                               | 1                           | 4            | 96.15                                | 91.58          | 20                                 |
| 09                                               | 6                           | 0            | 91.58                                | 64.10          | 14                                 |
| 12                                               | 1                           | 0            | 64.10                                | 59.52          | 13                                 |
| 15                                               | 2                           | 1            | 59.52                                | 49.60          | 10                                 |
| 18                                               | 2                           | 1            | 49.60                                | 38.58          | 7                                  |
| 21                                               | 1                           | 0            | 38.58                                | 33.07          | 6                                  |
| 24                                               | 0                           | 1            | 33.07                                | 33.07          | 5                                  |
| 27                                               | 0                           | 1            | 33.07                                | 33.07          | 4                                  |
| 30                                               | 0                           | 2            | 33.07                                | 33.07          | 2                                  |
| 33                                               | 0                           | 0            | 33.07                                | 33.07          | 2                                  |
| 36                                               | 1                           | 0            | 33.07                                | 16.53          | 1                                  |
| 39                                               | 0                           | 1            | 16.53                                | 0.00           | 0                                  |

See Figures 1 and 2 for dose intensity, overall survival, and progression-free survival data.
### ADVERSE EVENTS

| Adverse events                        | CTCAE grade 1, n (%) | CTCAE -grade 2, n (%) | CTCAE grade 3, n (%) | CTCAE grade 4, n (%) |
|---------------------------------------|----------------------|-----------------------|----------------------|----------------------|
| Chemistry disorders                   |                      |                       |                      |                      |
| Creatinine increased                  | 9 (33)               | 1 (4)                 |                      |                      |
| Elevated AST/ALT/alk phos             |                      |                       | 2 (7)                |                      |
| Hyperglycemia                         |                      | 6 (22)                |                      |                      |
| Hyperkalemia                          |                      | 1 (4)                 |                      |                      |
| Hypoalbuminemia                       | 1 (4)                |                       |                      |                      |
| Hypocalcemia                          |                      |                       | 1 (4)                |                      |
| Hypokalemia                           | 1 (4)                |                       |                      |                      |
| Hypomagnesemia                        | 2 (7)                |                       |                      |                      |
| Hyponatremia                          | 1 (4)                |                       |                      |                      |
| Total bilirubin increased             | 3 (11)               | 1 (4)                 |                      |                      |
| Ear and labyrinth disorders           |                      |                       |                      |                      |
| Hearing impaired                      | 3 (11)               | 1 (4)                 |                      |                      |
| Eye disorders                         |                      |                       |                      |                      |
| Blurred vision                        | 1 (4)                |                       |                      |                      |
| General disorders                     |                      |                       |                      |                      |
| Failure to thrive                     |                      |                       | 1 (4)                |                      |
| Fatigue                               | 2 (7)                | 2 (7)                 |                      |                      |
| Pain                                  | 1 (4)                | 1 (4)                 | 1 (4)                |                      |
| GI disorders                          |                      |                       |                      |                      |
| Diarrhea                              |                      |                       | 2 (7)                |                      |
| Dysphagia                             | 1 (4)                |                       |                      |                      |
| Mucositis                             |                      | 4 (15)                |                      |                      |
| Oral pain                             |                      | 1 (4)                 |                      |                      |
| Hematological                         |                      |                       |                      |                      |
| Anemia                                | 14 (52)              | 8 (30)                | 2 (7)                |                      |
| INR increased                         |                      | 1 (4)                 |                      |                      |
| Lymphocytopenia                       |                      | 19 (70)               | 2 (7)                |                      |
| Neutropenia                           | 2 (7)                | 6 (22)                | 2 (7)                |                      |
| Thrombocytopenia                      | 7 (26)               |                       |                      |                      |
| Infections                            |                      |                       |                      |                      |
| Abdominal infection with G-tube       |                      | 1 (4)                 |                      |                      |
| Catheter-related infection            |                      | 1 (4)                 |                      |                      |
| Sepsis                                |                      | 1 (4)                 |                      |                      |
| Sinusitis                             |                      | 1 (4)                 |                      |                      |
| UTI                                   |                      | 1 (4)                 |                      |                      |
| Nervous system disorders              |                      |                       |                      |                      |
| Dizziness                             | 1 (4)                |                       |                      |                      |
| Neuropathy                            | 8 (30)               | 1 (4)                 |                      |                      |
| Presyncope                            |                      |                       | 1 (4)                |                      |
| Psychiatric disorders                 |                      |                       |                      |                      |
| Anxiety                               | 1 (4)                |                       |                      |                      |
| Insomnia                              | 1 (4)                |                       |                      |                      |
| Respiratory disorders                 |                      |                       |                      |                      |
| Pneumonia                             |                      | 2 (7)                 |                      |                      |
| Cough                                 | 1 (4)                | 1 (4)                 |                      |                      |
| Hemoptysis                            | 1 (4)                |                       |                      |                      |
| Wheezing                              | 1 (4)                |                       |                      |                      |
We set out to conduct a trial of weekly docetaxel cisplatin (or carboplatin) and cetuximab in patients with metastatic or recurrent squamous cell carcinoma of the head and neck (SCCHN) in order to ask whether this combination of agents dosed on a weekly schedule could preserve response rates while diminishing toxicity in this patient population. We saw a 56% response rate (15/27 patients). Thirty-three percent (9/27 patients) had the responses confirmed with follow-up imaging per RECIST. Although this RECIST-based confirmed response rate was below our planned benchmark, it is worth noting that in the Vermorken and Gibson studies, which are regarded as definitive benchmarks for response to platinum, fluorouracil and cetuximab (PFC) and platinum and paclitaxel (PT), formal RECIST criteria were not used. Therefore, the response rate we observed with docetaxel, platinum, and cetuximab compares very favorably with these latter two studies, that is, 56% compared with 36% and 27% [4, 8]. Our median progression-free survival and overall survival rates of 4.8 months and 14.7 months compare favorably with both the above randomized control trials and multiple other chemotherapeutic regimens used in this setting [3].

The most remarkable observation we made was a very low rate of high-grade adverse events. Specifically, there were only two grade 4 adverse events described, both clinically insignificant lymphopenia. This number compares very favorably with prior studies, in which grade 4 adverse event rates ranged typically from 30% to 50% for chemotherapy doublets and triplets administered once every 21 days [4, 8, 12, 13]. Our adverse event (AE) data are consistent with another report of weekly docetaxel and cisplatin in this setting [14]. Although this diminution in high-grade adverse events is promising, we are uncertain as to whether it can be attributed to the substitution of a taxane for fluorouracil, the weekly dosing schedule, more frequent monitoring, or higher attention to supportive care in this single-institution study. We view these AE rate reduction results as very promising but preliminary, for it is impossible to say whether such results extrapolate to a larger multi-institutional experience.

With the emergence of promising new immunotherapy treatments (in particular the recent approvals of nivolumab and pembrolizumab for the treatment of SCCHN in the recurrent metastatic setting) it is difficult to predict what place chemotherapy will occupy in future clinical practice. It is worth remarking that monoclonal antibodies targeting PD-1 have limited activity in this disease, with a response rate of only 13% in the recently published randomized controlled trial for nivolumab [5]. We suspect that the greatest benefit to the new immunotherapy compounds, either alone or in combination with other immunotherapy compounds, is likely to be realized with treatment plans that integrate immunotherapy and conventional systemic therapy. Regimens less toxic than the EXTREME regimen or standard high-dose cisplatin will need to be tested in combination with immunotherapy in order to achieve the goal of maximal antitumor activity with a reasonable toxicity profile.

We believe our results seen in this patient population justify further development of this regimen. Given the changing landscape of treatment options in patients with head and neck cancer, it will be necessary to explore more definitive comparisons with the present chemotherapy standards while simultaneously exploring integration with immunotherapy.

### Author Contributions

**Conception/design:** Harlan Pinto, A. Dimitrios Colevas  
**Provision of study material or patients:** Harlan Pinto, Jonathan W. Riess, Richard Luciano, Jessie Coty, A. Dimitrios Colevas  
**Collection and/or assembly of data:** Vanessa Trieu, Jonathan W. Riess, Ruth Lira, Richard Luciano, Jessie Coty, A. Dimitrios Colevas  
**Data analysis and interpretation:** Vanessa Trieu, Jonathan W. Riess, Ruth Lira, Derek Boothroyd, A. Dimitrios Colevas  
**Manuscript writing:** Vanessa Trieu, A. Dimitrios Colevas  
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### Disclosures

Jonathan W. Riess: Takeda, Celgene, AbbVie, Axis, Physician Education Resource (C/A), Merck, AstraZeneca, Novartis, Millenium (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; (SAB) Scientific advisory board

| Skin and subcutaneous tissue disorders |  |
|----------------------------------------|---|
| Acneiform rash                          | 11 (41) |
| Nail discoloration                      | 1 (4) |
| Vascular disorders                     |  |
| Hypertension                           | 9 (33) |
| Pulmonary embolism*                    | 5 (19) |
| Worst overall                          | 23 (85) |

*Serious adverse events.

Abbreviations: AE, adverse event; alk phos, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; CTCAE, Common Terminology Criteria for Adverse Events; G-tube, gastrostomy tube; GI, gastrointestinal; INR, international normalized ratio; UTI, urinary tract infection.
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**FIGURES AND TABLES**

**Figure 1.** Dose intensity of chemotherapy administered as a percentage of intended dose per cycle. Patients who discontinued for progression of disease or who continued on cetuximab alone after cycle 7 are not represented in this figure. Patients who received cisplatin and carboplatin within the same cycle are counted separately in each bar for each agent, with intensity represented on a prorated basis for each. Abbreviation: pt, patient.

**Figure 2.** Survival graphs. (A): Overall survival. (B): Progression-free survival. Abbreviations: CI, confidence interval; OS, overall survival; PFS, progression-free survival.
Table 2. Baseline characteristics

| Characteristic                        | n (%)       |
|---------------------------------------|-------------|
| Gender                                |             |
| Male                                  | 23 (85)     |
| Female                                | 4 (15)      |
| Median age (range), years             | 60 (24–80)  |
| Primary tumor site                    |             |
| Oropharynx                            | 14 (52)     |
| p16+                                  | 11 (79)     |
| p16− or unknown                       | 3 (21)      |
| Oral cavity                           | 5 (19)      |
| Larynx                                | 4 (15)      |
| Nasal cavity                          | 1 (4)       |
| Nasopharynx                           | 3 (11)      |
| Previous therapy                      |             |
| Surgery                               | 14 (52)     |
| Radiation                             | 21 (78)     |
| Chemotherapy                          | 20 (74)     |
| Docetaxel                             | 6 (22)      |
| Cisplatin                             | 16 (59)     |
| 5-FU                                  | 4 (15)      |
| Cetuximab                             | 6 (22)      |
| Bevacizumab                           | 1 (4)       |
| Newly metastatic                      | 23 (85)     |
| Local recurrence                      | 4 (15)      |
| Relapsed following prior therapy      | 24 (89)     |
| No prior therapy                      | 3 (11)      |
| Median time from previous therapy (range), months | 5.9 (2.1–61.8) |
| Race                                  |             |
| White                                 | 17 (63)     |
| Black or African American             | 1 (4)       |
| Asian                                 | 5 (19)      |
| Not reported                          | 1 (4)       |
| Unknown                               | 3 (11)      |
| Ethnicity                             |             |
| Hispanic or Latino                    | 4 (15)      |
| Non-Hispanic                          | 23 (85)     |

Abbreviations: 5-FU, fluorouracil.