

A Randomized Phase II Study of Cetuximab Every 2 Weeks at Either 500 or 750 mg/m² for Patients With Recurrent or Metastatic Head and Neck Squamous Cell Cancer

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Abstract

Cetuximab is typically administered on a weekly schedule for patients with recurrent or metastatic head and neck squamous cell cancer (HNSCC). This study explores cetuximab administered every 2 weeks (q2w). In this multicenter randomized prospective phase II study, eligible patients (≤ 2 prior cytotoxic chemotherapy regimens for recurrent or metastatic disease; ECOG performance status ≤ 2) were randomized to receive cetuximab q2w at 500 mg/m² (Group A) or 750 mg/m² (Group B). The primary end point was response rate (RECIST 1.0). Sixty-one patients were enrolled: 35 in Group A and 26 in Group B, which was closed early for lack of efficacy. Confirmed partial response rates were 11% for Group A (4/35) and 8%

for Group B (2/26) according to intention to treat analysis. Partial responses occurred only among patients whose primary tumors were in the oral cavity or larynx. Median progression-free survival (PFS) and median overall survival (OS) were similar for both groups (PFS, 2.2 and 2.0 months; OS, 7.0 and 9.4 months; Groups A and B, respectively). The most common cetuximab-related adverse events (all grades) among treated subjects included rash, fatigue, and hypomagnesemia. Cetuximab, 500 mg/m², q2w achieves similar efficacy as conventional dosing for patients with recurrent or metastatic HNSCC. Escalating the dose to 750 mg/m² q2w offers no obvious therapeutic advantage. (*JNCCN* 2012;10:1391–1398)

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The epidermal growth factor receptor (EGFR) is expressed on virtually all head and neck squamous cell cancer (HNSCC) tumors, and high levels of expression have been associated with unfavorable clinical prognosis.^{1,2} Cetuximab is a chimeric IgG1 monoclonal antibody that binds to the extracellular domain of EGFR and inhibits ligand binding.^{3,4} In patients with recurrent or metastatic HNSCC, weekly cetuximab (initial dose of 400 mg/m² followed by weekly doses of 250 mg/m² intravenously) has been evaluated both as monotherapy and in combination with cytotoxic chemotherapy.⁵

Cetuximab weekly monotherapy for patients with advanced platinum-refractory HNSCC yielded objective radiographic responses rates of 10% to 13% in phase II studies.^{6,7} In a randomized phase III study for patients who had not received any prior chemotherapy for recurrent or metastatic HNSCC, subjects received either

cetuximab plus cisplatin or placebo plus cisplatin. The objective response rate favored the cetuximab arm (26% vs. 10%; $P=.03$). However, progression-free survival (PFS) and overall survival (OS) did not differ significantly between the groups.⁸

The addition of standard weekly cetuximab to platinum-based chemotherapy was evaluated in the EXTREME trial. Subjects ($n=442$) with recurrent or metastatic HNSCC were randomized to receive cisplatin (or carboplatin, per investigator's choice) plus 5-fluorouracil with or without weekly cetuximab. No prior therapy for recurrent or metastatic disease was allowed. The addition of cetuximab to the platinum plus 5-fluorouracil doublet was associated with significant improvements in response rate (36% vs. 20%), PFS (5.6 vs. 3.3 months), and OS (10.1 vs. 7.4 months).⁹

The early studies that established weekly dosing of cetuximab did not establish a maximum-tolerated dose,^{10,11} and subsequent studies explored other doses and schedules of cetuximab. These dose exploration studies were performed in patients with advanced colorectal cancer. One question was whether anti-tumor efficacy could be improved with dose escalation. A second issue was tolerability of every-2-week (q2w) dosing.

In pharmacokinetic studies of q2w dosing of cetuximab in patients with metastatic colorectal cancer, cetuximab doses of 400 to 700 mg/m² q2w were well tolerated and the maximum tolerated dose was not reached.¹² Pharmacokinetic analysis showed that trough levels for the 500 mg/m² q2w, 600 mg/m² q2w, and 250 mg/m² weekly regimens were comparable.^{12,13} Pharmacodynamic studies, in which subjects underwent skin biopsies at baseline and at week 4 showed that all cetuximab dose levels yielded comparable changes in the expression of phosphorylated EGFR (pEGFR), phosphorylated mitogen-activated protein kinase (pMAPK), Ki67, p27, and phosphorylated signal transducers and activators of transcription 3 (pSTAT3) as detected with immunohistochemistry.¹⁴ Based on this work and similar studies,^{15,16} cetuximab at 500 mg/m² q2w was identified as a convenient and feasible dose for patients with advanced colorectal cancer.

This study evaluates 2 doses of q2w cetuximab monotherapy, 500 and 750 mg/m², for patients with recurrent or metastatic HNSCC.

Methods

Study Objectives

The primary objective of this study was to evaluate the response rate of 2 separate doses of cetuximab as monotherapy in patients with recurrent or metastatic HNSCC. The secondary objectives of this study were to determine the disease control rate, OS, PFS, safety, and tolerability

Patient Population

Patients aged 18 years or older were eligible if they had histologically or cytologically confirmed HNSCC that was recurrent or metastatic, measurable disease as defined by RECIST,¹⁷ ECOG performance status of 2 or less, and adequate hematologic (absolute neutrophil count $\geq 1200/\mu\text{L}$, platelet count $\geq 100,000/\mu\text{L}$), hepatic (total bilirubin ≤ 1.5 mg/dL and transaminases and alkaline phosphatase ≤ 5 times the upper limit of normal), and renal function (serum creatinine ≤ 1.5 times the upper limit of normal or calculated creatinine clearance >40 mL/min). Key exclusion criteria included prior cetuximab therapy in the setting of recurrent or refractory disease, more than 2 prior cytotoxic chemotherapy regimens for metastatic/recurrent disease, uncontrolled central nervous system metastases, or other active invasive malignancies (other than nonmelanoma skin cancers or in situ cervical cancer).

Study Design

This was a multicenter, open-label, randomized, phase II study for patients with recurrent and/or metastatic HNSCC. The study was approved by the Institutional Review Boards at each of the participating institutions, and all subjects provided written informed consent.

Patients were randomized to receive cetuximab on Group A (500 mg/m² over 2 hours) or Group B (750 mg/m² over 3 hours) on day 1 and 15 of each 28-day cycle. Patients continued to receive treatment until disease progression or until other withdrawal criteria were met.

Toxicity Management and Response Assessment

Adverse events were graded according to the NCI Common Terminology Criteria for Adverse Events, version 3.0. Physical examination with assessment of adverse events was required at the start of each 4-week cycle. Toxicity management guidelines included dose delays for grade 3 adverse events (for up

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to 21 days), and removal from study for any attributable grade 4 toxicity or any hypersensitivity reaction of grade 3 or higher. Patients who maintained active follow-up were followed for at least 30 days after last cetuximab therapy. Radiologic imaging for RECIST assessment¹⁷ of indicator lesions was performed every 2 cycles (typically every 8 weeks) and/or after the final study treatment. All reported major responses were reviewed by the Department of Radiology at the lead site, Memorial Sloan-Kettering Cancer Center.

Statistical Considerations

Up to 70 patients total could be randomized to either Group A or Group B (up to 35 patients per group). The response rate for each group was tested against the historical control of 10%.¹⁸ A 2-stage Simon optimal design was used in each arm individually to test the null hypothesis that the response rate would be at most 10% versus the alternative that it would be 25% or greater (88.6% power for detection of a 25% response rate in each group). The study had a 12.4% overall type I error. The null hypothesis would be rejected if 6 or more tumor responses occurred among 35 patients in a group.

OS and PFS were analyzed using the Kaplan-Meier method, from which median times were estimated. OS was defined as the time from randomization until death, and PFS was defined as the time from randomization until progression or death. Primary analyses of response rate and survival followed the principle of intention-to-treat (ITT).

The study contained an early stopping rule for lack of efficacy. If 1 or fewer responses were observed after 18 patients per cohort were accrued and evaluated, then the null would be accepted and accrual to the group would be terminated early. Accrual to a given group was allowed to continue without interruption until 18 patients were evaluable in that group. The chance of early stopping under the null hypothesis was 45%, and the chance of early stopping under the alternative (eg, in error) was 4%. Because of the interval between enrollment and response evaluation, accrual beyond 18 subjects in a group was anticipated (and allowed) to occur, until enough patients (n=18) were evaluable for response and/or criteria were met for continued accrual beyond 18 subjects in the group.

Patients who were removed from the study before completing 2 cycles of treatment because of tox-

icity (or withdrawal of consent, or noncompliance) would not be considered evaluable for the efficacy-based early stopping rule. The early stopping rule for efficacy was based on the first 18 patients in each arm who completed at least 2 cycles of therapy. However, patients removed from the study because of disease progression during cycle 1 or 2 were counted toward the early stopping rule for efficacy.

To optimize patient safety, the protocol also contained an early stopping rule for safety that was independent of the efficacy-based early stopping rule. The early stopping rule for safety held that if 3 or more of the first 18 patients (each group treated separately) experienced a dose-limiting toxicity (as defined in the protocol) during cycle 1 or 2, that group would be closed because of excess toxicity.

Results

Patient Characteristics

The study enrolled 61 patients from 10 cancer centers across the United States. The first subject began treatment on February 8, 2008, and the final subject was registered on November 27, 2009. Thirty-five patients were enrolled in Group A and 26 patients were enrolled in Group B, which was closed early in accordance with the early stopping rule. Patient disposition is summarized in Figure 1. Table 1 summarizes baseline characteristics for all enrolled patients. Median age (59 years in Group A and 61 years in Group B), gender distribution (80% male in Group A and 92% male in Group B), and median performance status (ECOG 1 in Groups A and B) were similar between the groups. Oropharynx was the most common primary tumor site in both groups. Two patients, both in Group B, were enrolled but did not receive any study treatment. These 2 untreated patients are not included in the subsequent safety analyses. The cutoff date for this analysis was May 24, 2011.

Treatment Delivery and Acute Adverse Events

The median number of treatment cycles delivered was 2 for both groups (ranges, <1–13 for Group A; <1–15 for Group B). The most common cetuximab-related adverse events (all grades) among treated subjects included rash, fatigue, and hypomagnesemia. Table 2 presents nonhematologic toxicities that occurred in greater than one-third of patients (regardless of grade)

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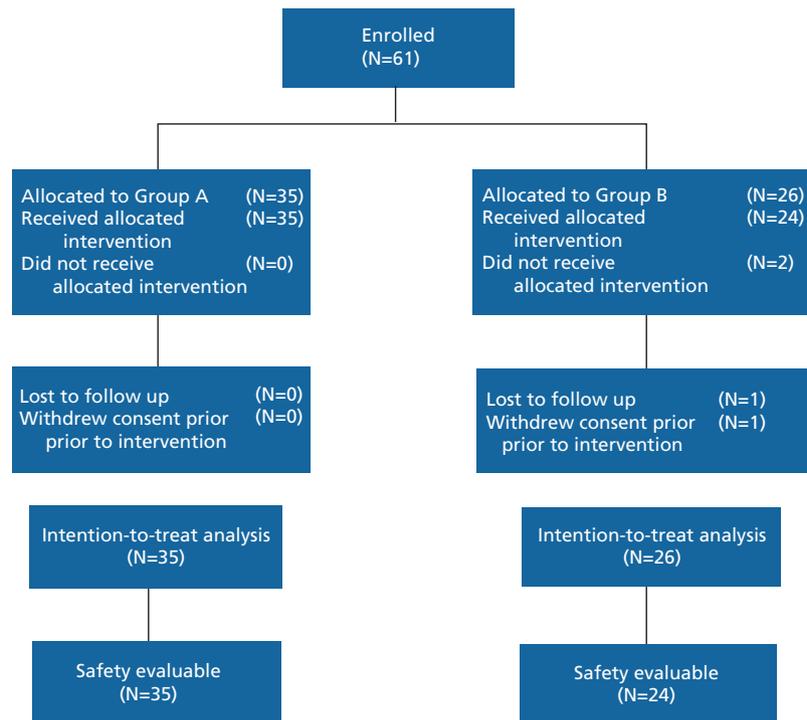


Figure 1 Consolidated Standards of Reporting Trials (CONSORT) diagram.

in either group, or which were scored as grade 3 or worse in at least 1 patient and believed to be possibly, probably, or definitely related to cetuximab. The incidence of hypomagnesemia (all grades) was higher in Group B (75%) than in Group A (40%). Of the 11 hypersensitivity reactions, 6 occurred at one site (Moffitt Cancer Center in Florida).

Efficacy

In Group A, the confirmed partial response rate was 11% (95% CI, 4.5%–26%) according to ITT analysis (4 partial responses among 35 subjects). One additional Group A patient had an unconfirmed partial response. In Group B, the confirmed response rate was 8% (95% CI, 2.1%–24.1%) according to ITT analysis (2 partial responses among 26 subjects). Group B was closed early because of insufficient efficacy according to the stopping rule, because only 1 partial response was observed among the first 18 patients who underwent radiologic response evaluation in Group B.

Table 3 summarizes the best response data for each group. The disease control rate (defined as response plus stable disease rate at the end of cycle 2) was 38% (95% CI, 26.6%–50%) for the entire study population according to ITT analysis. The disease

control rate was 46% in Group A (16/35 patients) and 27% in Group B (7/26 patients). No complete responses according to RECIST 1.0 were seen in either group.

The median follow-up for all patients was 24.5 months. Thirty-two deaths occurred in Group A and 20 in Group B. Median OS for patients was 7 months for patients in Group A (range, <1–26+ months; 95% CI for median, 6.1–8.1 months) and 9.4 months for patients in Group B (range, <1–32+ months; 95% CI for median, 3.9–10.6 months). Kaplan-Meier plots for OS are shown in Figure 2.

Median PFS was 2.2 months in Group A (range, <1–9.6 months; 95% CI for median, 1.8–3.7 months) and 2.0 months in Group B (range, <1–14.8 months; 95% CI for median, 1.8–5.3 months). Kaplan-Meier plots for PFS are shown in Figure 3. Survival analyses in Figures 2 and 3 are according to ITT (Group A, n=35; Group B, n=26).

Among the 6 patients with confirmed partial responses, the median duration from randomization until radiologic progression of disease or removal from study was 5.8 months (range, 5.5–13.5 months). Three patients experiencing response had primary tumors of the oral cavity, and 3 had primary tumors of the glottic larynx. Another patient in Group B

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with a tobacco history of 70 pack-years and base-of-tongue squamous cell cancer that had metastasized to the liver remained on treatment with stable disease (best response, 23% tumor reduction) for 14.6 months. No verified partial responses were observed among 25 patients with oropharynx primaries.

Discussion

The central finding of this study is that cetuximab at 500 mg/m² q2w (Group A) is well tolerated as palliative monotherapy for patients with recurrent or metastatic HNSCC, and efficacy (11% confirmed partial response rate) is comparable to that seen with conventional dosing of cetuximab in this patient population. Based on response rate, further escalation of cetuximab dose did not appear likely to increase efficacy for rejection of the null hypothesis. Therefore, Group B (8% confirmed partial response rate) was closed in accordance with the efficacy-based early stopping rule.

In Group A, acneiform rash was the most common toxicity of any grade (66%), and rash was also the most common grade 3 toxicity (11%). These findings are similar to the skin toxicity experiences reported in prior studies of standard weekly or 500 mg/m² q2w dosing of cetuximab. Among patients with advanced HNSCC receiving standard weekly cetuximab plus 5-fluorouracil in the EXTREME study, the incidence of grade 3 or higher skin reactions was 9%.⁹ In a retrospective study of biweekly cetuximab among patients (n=88) with advanced colorectal cancer, the incidence of grade skin toxicity was 15%.¹⁹

The 6 patients who experienced partial responses in this study all had primary tumor sites in either the oral tongue or glottic larynx. The nonoropharynx primary sites suggest that the tumors were unlikely to be human papillomavirus (HPV)-related,²⁰ although HPV testing of tumors was not required in this protocol. The results suggest a hypothesis that the efficacy of anti-EGFR antibodies against recurrent or metastatic HNSCC

Table 1 Patient Baseline Characteristics

Characteristic	Group A (N=35)	Group B (N=26)
Median age, y (range)	59 (46–84)	61 (37–77)
Gender (male/female)	28/7	24/2
Median ECOG performance status (range)	1 (0–2)	1 (0–2)
ECOG performance status	Patients (n)	Patients (n)
ECOG 0	11	10
ECOG 1	18	13
ECOG 2	6	3
Subsite		
Larynx	7	4
Oral cavity	7	5
Oropharynx	16	9
Hypopharynx	4	2
Paranasal sinus/nasal cavity	0	3
Nasopharynx	1	1
Neck node, unknown primary	0	2
Received prior radiotherapy	33	25
Received prior chemotherapy for recurrence or metastasis disease		
0 prior regimens	13	14
1 prior regimen	20	11
2 prior regimens	2	1

Table 2 Cetuximab-Related Adverse Events

Adverse Event	Group A (N=35)		Group B (N=24)	
	Any Grade (%)	≥ Grade 3 (%)	Any Grade (%)	≥ Grade 3 (%)
Rash, acneiform	23 (66)	4 (11)	18 (75)	0
Fatigue	16 (46)	0	13 (54)	0
Magnesium, low	14 (40)	0	18 (75)	1 (4)
Nausea	8 (23)	2 (6)	7 (29)	0
Hypersensitivity	8 (23)	3 (9)	3 (13)	2 (8)
Headache	6 (17)	2 (6)	4 (17)	0
Vomiting	6 (17)	2 (6)	3 (13)	0
ALT elevation	6 (17)	1 (3)	0	5 (21)
Nail changes	5 (14)	1 (3)	4 (17)	0
Desquamation	4 (11)	1 (3)	1 (4)	0
Muscle weakness	1 (3)	1 (3)	0	0
Syncope	0	0	1 (4)	1 (4)

Abbreviation: ALT, alanine aminotransferase.

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Table 3 Best Response				
Best Response	Group A		Group B	
	% (Events/ Number of Subjects)	95% CI	% (Events/ Number of Subjects)	95% CI
Partial response ^a	11.4 (4/35)	4.5–26.0	7.7 (2/26)	2.1–24.1
Stable disease	34.3 (12/35)	20.8–50.9	19.2 (5/26)	8.5–37.9
DCR ^b	45.7 (16/35)	30.4–61.8	27.0 (7/26)	13.7–46.1
Disease progression	40.0 (14/35)	25.6–56.4	46.2 (12/26)	28.8–64.5
Symptomatic deterioration ^c	14.3 (5/35)	6.3–29.4	15.4 (4/26)	6.2–33.5
Inevaluable ^d	0	N/A	11.5 (3/26)	N/A

Abbreviation: DCR, disease control rate; N/A, not applicable.

^aPartial response refers to confirmed partial responses according to RECIST 1.0.¹⁷

^bPartial response + stable disease rate at the end of cycle 2.

^cSymptomatic deterioration includes patients who came off study because of toxicity or clinical decline before the planned imaging assessment at the end of cycle 2.

^dThere were 3 inevaluable patients in Group B; 2 were enrolled in Group B but did not receive any study treatment and 1 was reported to have experienced partial response but, on central radiology review at the lead site in May 2011, was deemed inevaluable for response.

may be associated with factors such as primary tumor site and/or HPV status. This hypothesis should be directly tested in a prospective clinical study in which knowledge of tumor HPV status is a required study inclusion criterion.

For future studies, either response rate or OS could be appropriate primary end points. OS was at least comparable, if not superior, in Group B. However, the CIs for survival estimates in this study are wide, and Group B was closed early because of low response rate. The experience in this study suggests that further cetuximab dose escalation beyond 500 mg/m² q2w is unlikely to be associated with clinical benefit in this patient population. Because the study was not powered to evaluate OS as the primary end point, firm conclusions cannot be drawn regard-

ing survival between the groups. Studies centering on survival as a primary end point and evaluating dose escalation to 750 mg/m² q2w or higher could be justified.

This study does not address the combination of cetuximab at 500 mg/m² q2w with other cytotoxics in HNSCC, although these combinations have been evaluated in other solid tumor types.^{13,21,22} However, the efficacy and tolerability of cetuximab at 500 mg/m² q2w in this study for patients with advanced HNSCC, and the pharmacokinetic/pharmacodynamic similarities of q2w and conventional dosing described by others,^{12,14} suggest that it should be feasible to study this q2w cetuximab regimen in combination with cytotoxic chemotherapy in patients with head and neck cancer. Off-protocol, cetuximab monotherapy at 500

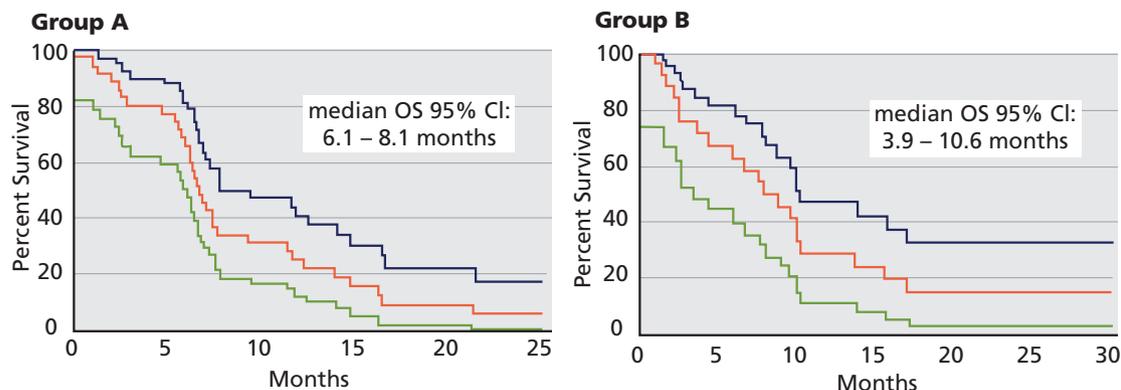


Figure 2 Kaplan-Meier plots for overall survival (OS) in Group A and Group B (orange lines) with 95% CIs (blue and green lines).

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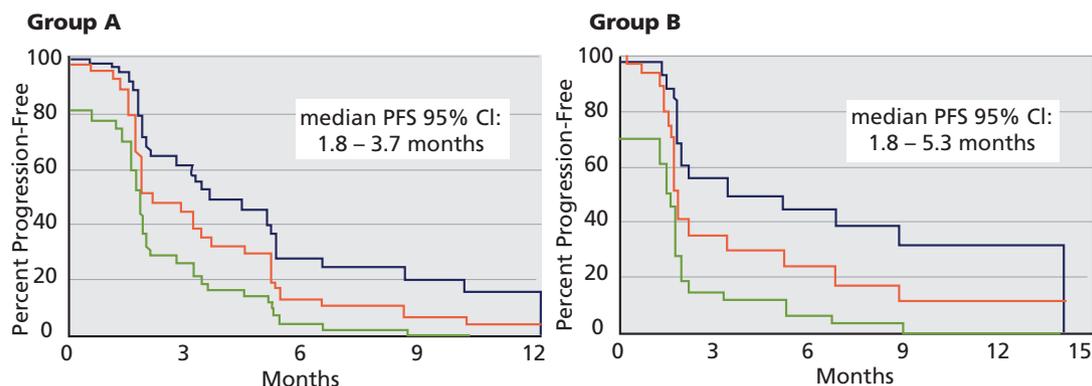


Figure 3 Kaplan-Meier plots for progression-free survival (PFS) in Group A and Group B (orange lines) with 95% CIs (blue and green lines).

mg/m² q2w is an appropriate palliative option for some patients with advanced HNSCC (eg, in those for whom exposure to the EXTREME regimen is not believed to be clinically indicated).

For patients with recurrent or metastatic HNSCC, cetuximab monotherapy at 500 mg/m² q2w appears similar to conventional weekly cetuximab in efficacy and tolerability, but further studies are needed to test equivalence directly. Future clinical studies in HNSCC also should seek to explore the combination of q2w cetuximab with radiation therapy and/or other chemotherapy regimens, and to evaluate whether HPV status impacts the efficacy of cetuximab among patients with recurrent or metastatic disease.

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