Patritumab with Cetuximab Plus Platinum-Containing Therapy in Recurrent or Metastatic Squamous Cell Carcinoma of the Head and Neck: An Open-Label, Phase-Ib Study

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M. Dillon, N. Brown, and Anne Jennings have no conflicts of interest to declare.

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Translational Relevance (147/120-150 words)

This study evaluates the safety, pharmacokinetics, and clinical activity of patritumab, a fully human anti–epidermal growth factor receptor 3 monoclonal antibody, in combination with cetuximab and a platinum agent for the treatment of recurrent and/or metastatic squamous cell carcinoma of the head and neck (SCCHN). Preclinical data have shown *in vitro* and *in vivo* activity with patritumab plus cetuximab in SCCHN. Data in this study showed that in patients with SCCHN, patritumab plus cetuximab with a platinum-based therapy was tolerated with patritumab and cetuximab pharmacokinetic profiles similar to historical single-agent values. Favorable responses were observed with a tumor response rate (complete response + partial response) of 47%. Further, this study recommends an 18-mg/kg loading dose of patritumab, followed by a 9-mg/kg maintenance dose every 21 days. These findings provide preliminary evidence for the possible use of patritumab plus cetuximab with platinum as first-line therapy in SCCHN.

Abstract (249/250 words)

Background: Patritumab plus cetuximab with platinum as first-line therapy for patients with recurrent and/or metastatic (R/M) squamous cell carcinoma of the head and neck (SCCHN) was evaluated for safety and to determine the recommended phase-II combination dose.

Methods: Patients aged ≥18 years with confirmed R/M SCCHN received intravenous patritumab (18-mg/kg loading dose [LD]); 9-mg/kg maintenance dose [MD] every 3 weeks [q3w]) + cetuximab (400-mg/m^2 LD; 250-mg/m^2 MD weekly) + cisplatin (100 mg/m^2 q3w) or carboplatin (area under the curve [AUC] of 5) for 6 cycles or until toxicity, disease progression, or withdrawal. Primary endpoints were dose-limiting toxicities (DLTs; grade ≥3 [21-day observation period]) and treatment-emergent adverse events (TEAEs). Pharmacokinetics, human antihuman antibodies (HAHA), tumor response, progression free survival (PFS), and overall survival (OS) were assessed.

Results: Fifteen patients completed a median (range) of 8.7 (2.0-20.7) patritumab cycles. No DLTs were reported. Serious AEs were reported in 9 patients (patritumab-related *n*=4). TEAEs (*N*=15 patients) led to patritumab interruption in 7 patients. Patritumab-related dose reductions were reported in 1 patient. Patritumab (18 mg/kg) pharmacokinetics (*N*=15) showed mean (standard deviation) $AUC_{0\text{-}21d}$ of 2,619 (560) µg·day/mL and maximum concentration of 499.9 (90.4) µg/mL. All patients were HAHA-negative at study end (single, transient low titer in 1 patient). Tumor response rate (complete plus partial response; *N*=15) was 47%. Median (95% confidence interval) PFS and OS (*N*=15) were 7.9 (3.7-9.7) and 13.5 (6.6-17.5) months, respectively.

Conclusion: Patritumab (18-mg/kg LD, 9-mg/kg MD) plus cetuximab/platinum was tolerable, active in SCCHN, and was selected as the phase II dose-regimen.

INTRODUCTION

Prognosis remains poor in patients with recurrent and/or metastatic (R/M) squamous cell carcinoma of the head and neck (SCCHN) (1); however, survival has improved with the use of cetuximab in this population (2–6). In patients treated in the first-line setting of R/M SCCHN, median progression-free survival (PFS) is approximately 4–6 months and median overall survival (OS) 10–15 months following first-line treatment with cetuximab in combination with chemotherapeutic agents (2–6). While cetuximab is effective in treating SCCHN, as well as colorectal cancer and non–small-cell lung cancer, many patients who initially respond, later develop resistance which limits efficacy (7,8). In cetuximab-resistant SCHHN cell lines, targeting the human epidermal growth factor receptor (HER) family, including EGFR, HER2, and HER3, resulted in an inhibition of proliferation (9).

Patritumab is a fully human anti–epidermal growth factor receptor 3 (HER3) monoclonal antibody that prevents heregulin-mediated HRG signaling by binding to the extracellular domain of HER3 (10)—thus inhibiting binding by the HER3 ligand heregulin—and promoting receptor internalization and degradation (11). HER3 receives signals from ligands, most importantly from heregulin (12,13), the binding of which induces the conformational change necessary for receptor dimerization of HER3 with HER family receptors, such as epidermal growth factor (EGFR) or HER2 (12–16).

High expression of heregulin is associated with HER3 signaling (17), which has been shown to be important for tumor growth and proliferation, including in cell lines for non–small-cell lung cancer (NSCLC) (18) and squamous cell carcinoma of the head and neck (SCCHN) (19). Heregulin expression has been shown to be up-regulated in cisplatin-resistant SCCHN cell lines (20). When combined with EGFR inhibitors (including cetuximab and panitumumab) in NSCLC and SCCHN cell lines and mouse models, patritumab enhanced anti-tumor activity and prevented HER3 activation following anti-EGFR treatment

(10,11,19). In a study by Wenzl et al., synergistic effects of patritumab with cetuximab on signaling were observed in 70% (7/10) of patritumab-responsive SCCHN cell lines. Furthermore, the combination of patritumab and cetuximab resulted in a stronger inhibition of proliferation and induction of apoptosis compared to either treatment alone (19). In the same study, significant partial or even complete tumor reduction was demonstrated in a head and neck mouse xenograft model when patritumab was administered as a single agent and in combination with cetuximab or panitumumab, respectively.

Given the evidence indicating enhanced *in vitro* and *in vivo* activity with patritumab plus cetuximab in SCCHN (19), combination therapy utilizing both targeted treatments may further improve efficacy in patients with R/M SCCHN. Therefore, in a phase Ib study, the safety and tolerability of first-line treatment with patritumab plus cetuximab with a platinum agent in patients with R/M SCCHN was investigated. Additionally, the recommended patritumab phase II dose was determined. The results of the phase Ib study are described herein.

METHODS

Overall study design

This was a multi-center, open-label, single-arm study of first-line treatment of patritumab plus cetuximab with platinum-based therapy in patients with recurrent or metastatic SCCHN (clinicaltrials.gov identifier: NCT02350712). This study was conducted in compliance with the International Conference on Harmonization, Guideline for Good Clinical Practice, and applicable national and local regulatory requirements. All patients provided written informed consent prior to participation in this study.

Patient eligibility

Adults (age ≥18 years) with Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1; histologically or cytologically confirmed recurrent disease or metastatic SCCHN originating from the oral cavity, oropharynx, hypopharynx, and larynx; and with adequate hematological, renal, and hepatic function were eligible for inclusion in this study.

Adequate hematologic function was defined as having an absolute neutrophil count ≥1.5 x 10^9/L, platelet count ≥100 x 10^9/L, and hemoglobin ≥10 g/dL. Adequate renal function was defined as having a calculated creatinine clearance ≥60 mL/minute. Adequate hepatic function was defined as having an aspartate aminotransferase and alanine aminotransferase ≤2.5 x upper limit of normal (ULN) (<5 x ULN if liver metastases are present), alkaline phosphatase ≤2.0 x ULN (<5 x ULN if bone or liver metastases are present), and bilirubin ≤1.5 x ULN. Patients also had prothrombin time or partial thromboplastin time ≤1.5 x ULN. Patients were to comply with the contraception requirements as specified in the study protocol or be of non-childbearing potential.

Patients were excluded if they had prior anti-EGFR, anti-HER2, anti-HER3, or anti-HER4 targeted therapy, prior treatment for recurrent and/or metastatic disease, history of other malignancies, except adequately treated non-melanoma skin cancer, curatively treated *in-situ* disease, or other solid tumors curatively treated with no evidence of disease for ≥5 years, history of active brain metastases, left ventricular ejection fraction <50%, or uncontrolled hypertension (systolic blood pressure >160 mmHg or diastolic blood pressure >100 mmHg).

Study objectives

The primary objectives were to evaluate the safety and tolerability of the combination of patritumab and cetuximab with cisplatin or carboplatin in the first-line treatment of patients with recurrent or metastatic SCCHN. An additional primary objective was to determine the recommended phase II dose for patritumab.

Secondary objectives included characterization of the pharmacokinetics (PK) of patritumab and of cetuximab (when co-administered with patritumab) and evaluation of the incidence and titer of human anti-human antibody (HAHA) formation (anti-patritumab antibodies). Partial and complete response rates, PFS and OS were also assessed.

Treatment

All patients received intravenous patritumab (18-mg/kg loading dose; 9-mg/kg maintenance dose) every 3 weeks plus cetuximab (400-mg/m^2 loading dose; 250-mg/m^2 maintenance dose) weekly plus cisplatin (100 mg/m^2) every 3 weeks or carboplatin (area under the curve [AUC] of 5) for 6 cycles **(Supplementary Fig. S1)**. The choice of platinum chemotherapy (cisplatin or carboplatin) was at the discretion of the investigator. Treatment cycles were 21 days, and patritumab and cetuximab could be continued beyond 6 cycles. Treatment was continued until disease progression, evidence of toxicity, or withdrawal from the study. Patients were permitted to continue treatment in the extension phase of this study, which began after the recommended phase II dose was defined and all patients had completed platinum-based treatment.

Patritumab dose de-escalation

Six to 9 patients were expected to be treated at the first dose levels (fewer than 6 if 3 or more patients experienced a dose limiting toxicity [DLT], in accordance with a 6+3 dose–de-escalation design). If ≤1 of the first 6 DLT-evaluable patients experienced a DLT after all patients completed the DLT observation period (i.e., the first treatment cycle), the current dose of patritumab was defined as the maximum tolerated dose (MTD) and thus the recommended phase II dose. However, if 2 of the first 6 patients experienced a DLT, then the cohort was expanded to 9 patients at the same dose level; if 2 of those 9 patients experienced a DLT, that current dose of patritumab was defined as the recommended phase II dose. If ≥3 patients experienced DLTs at any dose level, the MTD would have been exceeded and a lower patritumab loading dose (based on safety and PK data) could have been explored. If the patritumab 18 mg/kg loading dose level was not tolerated based on observations of DLTs, for subsequent patients a lower loading dose of patritumab (15 mg/kg) and 9-mg/kg maintenance dose would have been administered in combination with cetuximab plus cisplatin or carboplatin every 3 weeks.

The schedule of patritumab dosing was based on patient trough levels that corresponded to maximal preclinical efficacy, as measured in the phase I study of patritumab in patients with advanced solid tumors. (21) Patritumab also had a favorable tolerability profile as a single agent in solid tumors (21) and when combined with erlotinib in a phase I study of NSCLC. (22) In the phase I combination NSCLC study, with the exception of a slightly higher incidence of any grade treatment-emergent adverse events (TEAEs), such as diarrhea, the types of TEAEs and incidence of grade ≥3 AEs observed were generally similar (22) to those observed in a phase II study of erlotinib monotherapy (23). Therefore, there was supporting rationale that the starting schedule would be well tolerated and provide adequate exposure, and hence a dose de-escalation design was selected that would minimize exposing patients to potentially sub-therapeutic levels of patritumab.

Study endpoints

Primary endpoints included evaluation of the incidence of DLTs (used to identify the MTD); the number of patients reporting the frequency and severity of TEAEs; the safety and tolerability of the combination of patritumab plus cetuximab and cisplatin or carboplatin; and the number of patients experiencing clinically significant or grade ≥3 changes in clinical laboratory evaluations, ECGs, echocardiograms, vital signs, and physical examinations.

Secondary endpoints included PK of serum patritumab and cetuximab, and the incidence and titer of HAHA formation. Other endpoints included tumor response, and PFS and OS.

Study assessments

Assessments occurred at predefined timepoints throughout the study, as described in **Supplementary Table S1**. Adverse events (AEs), including TEAEs and serious AEs (SAEs) were assessed per Common Terminology Criteria for Adverse Events (CTCAE; Version 4.03) and the Medical Dictionary for Regulatory Activities (MedDRA; Version 17.0). DLTs were defined as any patritumab-related grade ≥3 hematological or non-hematological toxicity occurring during the DLT observation period (days 1–21), unless clearly attributed to causes other than patritumab treatment (not including alopecia, anorexia, fatigue [grade 1 or 2], and nausea and vomiting in absence of standard anti-emetic therapy). PK assessments of serum patritumab and cetuximab included the area under the plasma drug concentration-time curve (AUC) from days 0–21 ($AUC_{0–21}$), AUC from days 0 to infinity ($AUC_{0–inf}$), half-life ($T_{1/2}$), maximum concentration (C_{max}), and time to maximum concentration (T_{max}). Tumor response (i.e., complete response, partial response, stable disease, and progressive disease) was assessed via RECIST criteria Version 1.1. PFS was defined as the time from the treatment start date to the date of the first radiographic disease

progression or death due to any cause. OS was defined as the time from treatment start date to death from any cause.

Patients who discontinued the study for any reason were followed for 40 days after their last dose to assess the presence of HAHA and other AEs. Any patients who were positive for neutralizing antibodies required follow-up testing every 3 months for up to 1 year following the last dose and until titers returned to baseline or until the start of another cancer therapy.

Statistical considerations and analysis

The total sample size was not based on formal statistical power calculations; sample size was dependent on the number of patritumab dose levels tested and observations of DLTs. The study was expected to enroll 6–18 DLT-evaluable subjects in accordance with a 6+3 dose de-escalation design. The number of DLTs among the DLT-evaluable subjects were summarized for each dose of patritumab evaluated in combination with cetuximab plus cisplatin or carboplatin. Safety analyses were descriptive and presented in tabular format with the appropriate summary statistics. Serum concentrations for patritumab and cetuximab and PK parameters were summarized with descriptive statistics. PFS and OS (analyzed ad hoc) and 95% CIs were estimated using Kaplan-Meier analysis.

RESULTS

Patient disposition

Patients were recruited between December 2014 and November 2015. Of the 17 subjects screened, 15 patients enrolled and initiated treatment **(Supplementary Table S2)**. As of December 21, 2016, 9 of the 15 patients had completed the study treatment per protocol and continued into the extension phase for treatment with patritumab plus cetuximab. Overall, 6 patients discontinued from the study treatment

phase due to progressive disease per RECIST criteria (*n*=3), death (*n*=1; due to cardiac arrest, considered related to cetuximab and carboplatin), a serious adverse event (*n*=1; bowel perforation, resolved; considered related to patritumab and cetuximab), and spinal surgery due to a collapsed disc (*n*=1; due to a prior work-related injury).

Patient demographics and baseline characteristics

Of the 15 patients treated and included in the study, the median (range) age was 53 (31–65) years with a median (range) time to diagnosis of R/M disease of 25.2 (4.9–133.4) months **(Table 1)**.

Most (93%, *n*=14) patients had tumor stage 3 or 4 SCCHN and an ECOG performance status of 1 (87%, *n*=13). The majority of patients had prior treatment with radiation therapy (93.3%, *n*=14) and induction/concomitant systemic cancer therapy (53%, *n*=8).

Treatment exposure and DLTs

The median (range) number of treatment cycles was 8.7 (2.0–20.7) for patritumab, 8.7 (2.0–20.7) for cetuximab, 4.5 (2.0–7.3) for carboplatin, and 6.3 (3.7–8.3) for cisplatin **(Supplementary Table S3)**. Over the course of the study, the cumulative median (range) dose was 5,339.7 (1,710.0–11,259.0) mg for patritumab, 10,442.5 (2,481.4–22,874.9) mg for cetuximab, 2695.0 (830.0–4,150.0) mg for carboplatin, and 960.0 (520.4–1,136.5) mg for cisplatin **(Supplementary Table S3)**. No DLTs were reported. Thus, there was no need for an additional cohort at a de-escalated dose.

Safety

T*reatment-emergent SAEs and TEAEs*

Treatment-emergent SAEs were reported in 9 (60%) patients overall; in 6 (40%) patients SAEs were CTCAE grade ≥3 **(Table 2).** SAEs were considered related to patritumab, cetuximab, cisplatin, or

carboplatin in 27% (*n*=4), 33% (*n*=5), 20% (*n*=3), and 27% (*n*=4) of patients, respectively. CTCAE grade ≥3 TEAEs were reported in all 15 patients **(Table 3).** TEAEs considered related to patritumab **(Table 3)**, cetuximab, cisplatin, or carboplatin were reported in 93% (*n*=14), 100% (*n*=15), 53% (*n*=8), and 67% (*n*=10) of patients, respectively. The most commonly reported TEAEs (any grade) overall (93% [*n*=14] of patients) or considered related to patritumab (73% [*n*=11] of patients) were skin and subcutaneous tissue disorders, the majority of which were considered to be CTCAE grade <3 in severity. TEAEs led to patritumab interruption in 7 (47%) patients, which was considered related to patritumab in 5 (33%) patients.

TEAEs leading to patritumab dose interruption included grade 3 anemia, grade 3 hypokalemia, and grade 2 weight loss (occurring in 1 patient); grade 3 hypomagnesemia, grade 2 leukopenia, and grade 1 neutropenia (occurring in a second patient); grade 4 acneiform rash, grade 3 aspiration pneumonia; grade 3 dehydration, grade 3 diarrhea, and grade 1 thrombocytopenia (occurring in a third, fourth, fifth, sixth, and seventh patient, respectively).

Patritumab dose reduction was reported in 1 (7%) patient with unresolved grade 1 mucositis, and was considered related to patritumab, cetuximab, and cisplatin.

Development of HAHAs

All patients were HAHA-negative at study end; however, a single, transient positive result with a low titer (<1:10) was reported for 1 patient on day 1 of cycle 2.

Pharmacokinetics

All patients were included in the PK analysis set. PKs for loading doses of patritumab (18 mg/kg) and cetuximab (400 mg/m^2) are shown in **Supplementary Table S4.** For patritumab, the mean (SD) $AUC_{0\text{-}21}$, AUC_{inf}, and C_{max} were 2,619 (560) µg·day/mL, 2,957 (720) µg·day/mL and 499.9 (90.4) µg/mL, respectively. The median (range) T_{max} values were 2.8 (1.0–6.1) hours. The estimated mean (SD) $t_{1/2}$ values were 6.6 (2.1) days. For cetuximab, the mean (SD) $AUC_{0\text{-}21}$, AUC_{inf}, and C_{max} were 706 (161) µg·day/mL, 800 (259) µg·day/mL, and 246.7 (48.3) µg/mL, respectively. The median (range) T_{max} values were 2.6 (1.0–5.0) hours. The estimated mean (SD) $t_{1/2}$ values 2.8 (0.4) days.

At the end of cycle 1, day 1, mean (SD) patritumab concentration was 460.3 (75.9) µg/mL, remaining relatively stable through 6 hours post-infusion, decreasing to 352.6 (65.6) µg/mL at 24-hours, 295.1 (62.5) µg/mL at 48-hours, and 125.0 (36.9) µg/mL at 168 hours post-infusion; by 480 hours, patritumab concentration decreased to 76.1 (119.4) µg/mL **(Fig. 1A)**. During the same timeframe, mean (SD) cetuximab concentration was 195.8 (51.1) µg/mL at the end of the first infusion, increasing slightly over the next 6 hours, and then decreasing to 160.1 (32.0) µg/mL at 24 hours, 120.0 (29.2) µg/mL at 48 hours, and finally 40.9 (13.1) µg/mL at 168 hours post-infusion **(Fig. 1B)**.

Efficacy

Tumor response

The tumor response rate (complete response + partial response) for all 15 patients was 47%. **(Fig. 2 and Supplementary Table S5).** Overall, 3 (20%) patients had a complete response, 4 (27%) had a partial response, and 8 (53%) had stable disease. Duration of response ranged from 8.3 to 55.6 weeks for patients with complete and partial response. Duration of stable disease ranged from 5.6 to 47.6 weeks for patients with stable disease.

The best (minimum) percent change in sum of diameters from baseline in target lesions for each patient is illustrated in **Fig. 3.** Of the 15 patients included in this study, the majority had local recurrence (n=11), 3 patients had distant metastasis (n=1 lung, n=1 lung and mediastinum, n=1 liver), and 1 patient had both local recurrence and distant metastasis (lymph node and lung). All 3 patients who had a complete response had locoregional recurrence. Of the patients who had a partial response, 2 had locoregional recurrence and 2 had distant metastasis.

PFS and OS

The median PFS for all patients was 7.9 (95% CI 3.7–9.7) months **(Supplementary Table S5)**. When analyzed over time, the PFS rate (95% CI) at 3, 6, 9, and 12 months was 87% (54–96%), 55% (25–77%), 39% (14–63%), and 8% (0.5–30%), respectively **(Supplementary Fig. S2A)**.

The median OS for all patients was 13.5 (95% CI 6.6-17.5) months **(Supplementary Table S5)**. When analyzed over time, the OS rate (95% CI) at 6, 12, and 18 months was 93% (61–99%), 53% (26–74%), and 27% (8–50%), respectively **(Supplementary Fig. S2B)**.

DISCUSSION

Options are limited in patients with R/M SCCHN; however, data from preclinical and clinical studies indicate that patritumab, in combination with cetuximab, may have improved benefit, compared with individual agents alone. In this phase Ib study in patients with R/M SCCHN, treatment with patritumab plus cetuximab with platinum-based therapy was tolerated and manageable. No DLTs were reported, and dose reductions due to a patritumab-related TEAE were reported in only 1 patient. All patients

remained HAHA-negative at the end of the study. The recommended phase II dose of patritumab, therefore, remains an 18-mg/kg loading dose, followed by a 9-mg/kg maintenance dose every 21 days.

When comparing the PK profile of patritumab and cetuximab with historical data the mean (SD) C_{max} of cetuximab for the 400 mg/m^2 dose in combination with patritumab (246.7 [48.3] µg/mL) was similar compared with the mean C_{max} from published studies of cetuximab PK alone (205.0 [65.7] µg/mL) (24). In addition, the mean (SD) AUC_{inf} of cetuximab in combination with patritumab (800.0 [259.0] µg•day/mL) was similar to the historical values (791.7 [325.1] µg·day/mL) (24). The mean (SD) C_{max} of patritumab was 499.9 (90.4) µg/mL in this study, similar to historical mean (SD) C_{max} of 539.7 (135.3) µg/mL for patritumab [Daiichi Sankyo, data on file]. The mean (SD) AUC_{inf} of patritumab was 2,957 (720) µg/mL in this study, similar to historical mean (SD) AUC_{inf} of 3,151.8 (796) µg/mL for patritumab [Daiichi Sankyo, data on file]. However, population PK analysis is needed to confirm similar exposure between studies since body weight, an important covariate on volume of distribution and clearance, may have different distributions across the populations. The observed mean (SD) $t_{1/2}$ of patritumab (6.61 [2.12] days) was slightly shorter, but comparable to historical data (mean [SD] 8.98 [1.62] days) (25). Similarly, the mean (SD) $t_{1/2}$ of cetuximab (2.8 [0.4] days [i.e., 67.2 [8.6] hours]) was shorter than data from Delgado et al of cetuximab alone (mean 4.4 [range 3.3–6.7] days at week 3) (26), and data reported in the cetuximab prescribing information (mean 4.8 [range 3.1–7.8] days) (27), but similar to data reported by Tan et al (mean 3.1 [SD 0.66] days following single 2-hour infusion) (24).

A favorable tumor response was also observed in the current study. Overall, median PFS was 7.9 months for all patients with 20% of patients achieving a complete response and 47% achieving overall response. In comparison, in a phase III (5) and a phase II (28) study of patients with R/M SCCHN who were treated with cetuximab plus cisplatin, median PFS was 4.2 and 6.0 months and overall response was 26% and

42%, respectively (CR was achieved by 5% of patients in the phase II study and not reported in the phase III study). The median OS of 13.5 months in this current small study population is potentially promising. Preliminary data from the follow-up phase 2 trial (clinicaltrials.gov identifier: NCT02633800) was reported at the 2018 Annual Meeting of the American Society of Clinical Oncology (29).

Limitations

There are several limitations of this study. Notably, this study included a small group of selected (not random) and relatively young (range: 31–65 years) group of patients. Further, this was an open-label study with no comparator and, therefore, tumor responses may not be representative of all patients with relapsed/metastatic SCCHN. Also, whilst we recognize that SCCHN is a heterogeneous disease, the relatively small number of patients in this study preclude investigation of tumor response and safety by the major tumor subsites represented (ie, oral cavity, oropharynx, and larynx). The collection of biomarker samples was not required in this study. However, this was a phase Ib study evaluating the safety and tolerability of patritumab plus cetuximab and a platinum-based therapy and provides evidence for future clinical studies.

Conclusions

Overall, the combination of patritumab with cetuximab and platinum therapy was tolerated, active in patients with R/M SCCHN, and did not appear to have a significant effect on the PK of cetuximab based on the non-compartmental analysis.

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Figure Legends

Figure 1.

A, Mean plasma concentration of patritumab (18 mg/kg loading dose), by time. **B**, Mean plasma concentration of cetumximab (400 mg/m^2 loading dose), by time.

Figure 2.

Tumor response and treatment duration (swimmer plot). AE, adverse event; CR, complete response; PR, partial response. [a]Includes neck (n=6), neck and lymph nodes (n=1), oral (n=1), tongue (n=1), tongue and oropharynx (n=1), tonsil and lymph node (n=1) tumors.

[b]Includes lung (n=1), lung and mediastinum (n=1), and liver (n=1) tumors.

[c]Includes lymph node and lung tumors (n=1).

Figure 3.

Best (minimum) percent change in sum of diameters from baseline in target lesions (safety analysis population). Dotted line represents response (-30) and disease progression (+20). [a]Includes 1 patient with moderately differentiated squamous cell carcinoma of the supraglottis. CR, complete response; PR, partial response; SD, stable disease.

Tables and Figures

Table 1. Baseline demographics and disease characteristics

Characteristic	***N*=15**
Age, years, median (range)	53.0 (31–65)
Sex, male, *n* (%)	15 (100)
Race, *n* (%)	
White	13 (86.7)
Asian	2 (13.3)
ECOG performance status, *n* (%)	
0	2 (13.3)
1	13 (86.7)
Primary disease site, *n* (%)	
Oral cavity	6 (40.0)
Oropharynx	5 (33.3)
Larynx	3 (20.0)
Other	1 (6.7)
Histologic grade, *n* (%)	
Well-differentiated	1 (6.7)
Moderately differentiated	5 (33.3)
Poorly differentiated	3 (20.0)
Unknown	6 (40.0)
Tumor stage at study entry	
1	1 (6.7)
3	7 (46.7)

4A–C	7 (46.7)
HPV status in patients with oropharyngeal disease (n=5)	
Positive	3 (60.0)
Negative	1 (20.0)
Unknown	1 (20.0)
Smoking status	
Current/Active	1
Former	8
Never	4
Unknown	2
Target tumor location	
Locoregional recurrence	11 (73.3)
Distant metastases	3 (20.0)
Locoregional recurrence + distant metastases	1 (6.7)
Time from SCCHN diagnosis to study treatment, months, median (range)	25.2 (4.9–133.4)
Prior systemic cancer therapy, *n* (%)	8 (53.3)
Radiation with chemotherapy	7 (46.7)
Best response to prior systemic cancer therapy, *n* (%)	
Complete response	5 (33.3)
Partial response	0 (0.0)
Stable disease	1 (6.7)
Progressive disease	1 (6.7)
Prior radiation therapy, *n* (%)	14 (93.3)

Abbreviations: ECOG, Eastern Cooperative Oncology Group; HPV, human papillomavirus; SCCHN, squamous cell carcinoma of the head and neck.

Table 2. All SAEs (*N*=15 patients)

SAE	Number of patients with an SAE, *n* (%)							
	All SAEs				SAEs related to patritumab			
	All grades	Grade 1	Grade 2	Grade ≥3	All grades	Grade 1	Grade 2	Grade ≥3
Any SAE	9 (60.0)	1 (6.7)	2 (13.3)	6 (40.0)[a]	4 (26.7)	1 (6.7)	0	3 (20.0)[a]
SAE, by preferred term								
Hypokalemia	4 (26.7)	0	1 (6.7)	3 (20.0)[b]	1 (6.7)	0	0	1 (6.7)[b]
Dehydration	2 (13.3)	0	0	2 (13.3)[b]	2 (13.3)	0	0	2 (13.3)[b]
Lower respiratory tract infection	2 (13.3)	1 (6.7)	0	1 (6.7)[b]	0	0	0	0
Vomiting	2 (13.3)	0	1 (6.7)	1 (6.7)[b]	0	0	0	0
Anemia	1 (6.7)	0	0	1 (6.7)[b]	1 (6.7)	0	0	1 (6.7)[b]
Cardiac arrest	1 (6.7)	0	0	1 (6.7)[c]		0	0	
Dysphagia	1 (6.7)	0	0	1 (6.7)[b]	0	0	0	0
Gastrointestinal hemorrhage	1 (6.7)	0	0	1 (6.7)[b]	1 (6.7)	0	0	1 (6.7)[b]
Intestinal perforation	1 (6.7)	0	0	1 (6.7)[d]	1 (6.7)	0	0	1 (6.7)[d]

Laryngeal repair	1 (6.7)	0	1 (6.7)	0	0	0	0	0
Pneumonia aspiration	1 (6.7)	0	0	1 (6.7)[b]	0	0	0	0
Post procedural hemorrhage	1 (6.7)	1 (6.7)	0	0	0	0	0	0
Stomatitis	1 (6.7)	1 (6.7)	0	0	1 (6.7)	1 (6.7)	0	0

[a]All SAEs: CTCAE grade 3 (*n*=4), grade 4 (*n*=1), and grade 5 (*n*=1); patritumab-related SAEs: CTCAE grade 3 (*n*=1), grade 4 (*n*=1), and grade 5 (*n*=1).

[b]CTCAE grade 3.

[c]CTCAE grade 5 (cardiac arrest).

[d]CTCAE grade 4.

Abbreviations: CTCAE, Common Terminology Criteria for Adverse Events v4.03; SAE, serious adverse event.

Table 3. TEAEs (in ≥2 patients) and TEAEs grade ≥3 (≥1 patient) (*N*=15)

TEAE	Number of patients with a TEAE, *n* (%)			
	All TEAEs		TEAEs related to patritumab	
	All grades	Grade ≥3	All Grades	Grade ≥3
Any TEAE	15 (100)	15 (100)[a]	14 (93.3)	8 (53.3)[a]
TEAE, by preferred term				
Skin and subcutaneous tissue[b]	14 (93.3)	4 (26.7)[c]	11 (73.3)	1 (6.7)[d]
Paronychia	12 (80.0)	0	8 (53.3)	0
Diarrhea	11 (73.3)	2 (13.3)[e]	4 (26.7)	2 (13.3)[e]
Hypokalemia	10 (66.7)	5 (33.3)[f]	4 (26.7)	2 (13.3)[e]
Fatigue	9 (60.0)	2 (13.3)[e]	2 (13.3)	1 (6.7)[e]
Hypomagnesemia	9 (60.0)	2(13.3)[e]	3 (20.0)	0
Leukopenia	8 (53.3)	0	4 (26.7)	0
Neutropenia	8 (53.3)	2 (13.3)[e]	4 (26.7)	0
Nausea	7 (46.7)	0	1 (6.7)	0
Anemia	6 (40.0)	2 (13.3)[e]	1 (6.7)	1 (6.7)[e]
Cheilitis	6 (40.0)	0	3 (20.0)	0
Constipation	6 (40.0)	0	1 (6.7)	0
Decreased appetite	6 (40.0)	0	1 (6.7)	0
Hiccups	4 (40.0)	0	0	0
Stomatitis	5 (33.3)	0	3 (20.0)	0
Dyspepsia	4 (26.7)	0	0	0
Mucosal inflammation	5 (33.3)	1 (6.7)[e]	4 (26.7)	1 (6.7)[e]
Vomiting	5 (33.3)	1 (6.7)[e]	0	0

Lower respiratory tract infection	4 (26.7)	1 (6.7)[e]	0	0
Tinnitus	4 (26.7)	0	0	0
Weight decreased	4 (26.7)	0	1 (6.7)	0
Xerosis	4 (26.7)	1 (6.7)[e]	2 (13.3)	1 (6.7)[e]
Dysgeusia	3 (20.0)	0	0	0
Dysphagia	3 (20.0)	2 (13.3)[e]	0	0
Hyperesthesia	3 (20%)	0	1 (6.7%)	0
Oral candidiasis	3 (20.0)	0	1 (6.7)	0
Peripheral sensory neuropathy	3 (20.0)	0	0	0
Pyrexia	3 (20.0)	0	0	0
Stoma site infection	3 (20.0)	0	0	0
Cough	2 (13.3)	0	0	0
Dehydration	2 (13.3)	2 (13.3)[e]	2 (13.3)	2 (13.3)[e]
Dizziness	2 (13.3)	0	0	0
Dyspnea	2 (13.3)	0	0	0
Facial neuralgia	2 (13.3)	0	0	0
Insomnia	2 (13.3)	0	0	0
Muscle spasms	2 (13.3)	0	0	0
Neuralgia	2 (13.3)	0	0	0
Cardiac arrest	1 (6.7)	1 (6.7)[g]	0	0
Dysphonia	1 (6.7)	1 (6.7)[e]	0	0
Folliculitis	1 (6.7)	1 (6.7)[e]	1 (6.7)	1 (6.7)[e]
Gastrointestinal hemorrhage	1 (6.7)	1 (6.7)[e]	1 (6.7)	1 (6.7)[e]

General physical health deterioration	1 (6.7)	1 (6.7)[e]	0	0
Hyperglycemia	1 (6.7)	1 (6.7)[e]	0	0
Hypophosphatemia	1 (6.7)	1 (6.7)[e]	0	0
Pneumonia aspiration	1 (6.7)	1 (6.7)[e]	0	0

[a]All TEAEs: CTCAE grade 3 (*n*=10), grade 4 (*n*=4), and grade 5 (*n*=1); patritumab-related TEAEs: CTCAE grade 3 (*n*=6) and grade 4 (*n*=2).

[b]Skin and subcutaneous tissue disorders for all TEAEs includes: 1 dermatitis (grade 1), 9 dermatitis acneiform (1 grade 1, 5 grade 2, 2 grade 3, and 1 grade 4), 1 dry skin (grade 1), 1 eczema (grade 2), 2 erythema (grade 2), 1 excessive granulation tissue (grade 1), 2 onycholysis (grade 1), 2 palmar-plantar erythrodysesthesia syndrome (grade 1), 4 pruritus (1 grade 1; 3 grade 2), 2 rash (1 grade 2; 1 grade 3), 1 rash erythematous (grade 1), 2 rash maculo-papular (1 grade 1; 1 grade 2), 6 skin fissures (5 grade 1; 1 grade 2), 1 skin toxicity (grade 2), 1 telangiectasia (grade 1), and 1 xeroderma (grade 1); for patritumab-related TEAEs includes: 1 dermatitis (grade 1), 5 dermatitis acneiform (1 grade 1; 3 grade 2; 1 grade 4), 1 dry skin (grade 1), 1 rash (grade 2), 1 rash erythematous (grade 1), 2 rash maculo-papular (1 grade 1; 1 grade 2), 2 skin fissures (1 grade 1; 1 grade 2), 1 skin toxicity (grade 2), and 1 xeroderma (grade 1).

[c]Three grade 3 and one grade 4.

[d]CTCAE grade 4.

[e]CTCAE grade 5 (cardiac arrest).

[f]Three grade 3 and 2 grade 4.

[g]CTCAE grade 3.

Abbreviations: CTCAE, Common Terminology Criteria for Adverse Events v4.03; TEAE, treatment-emergent adverse event**.**

Figure 1.

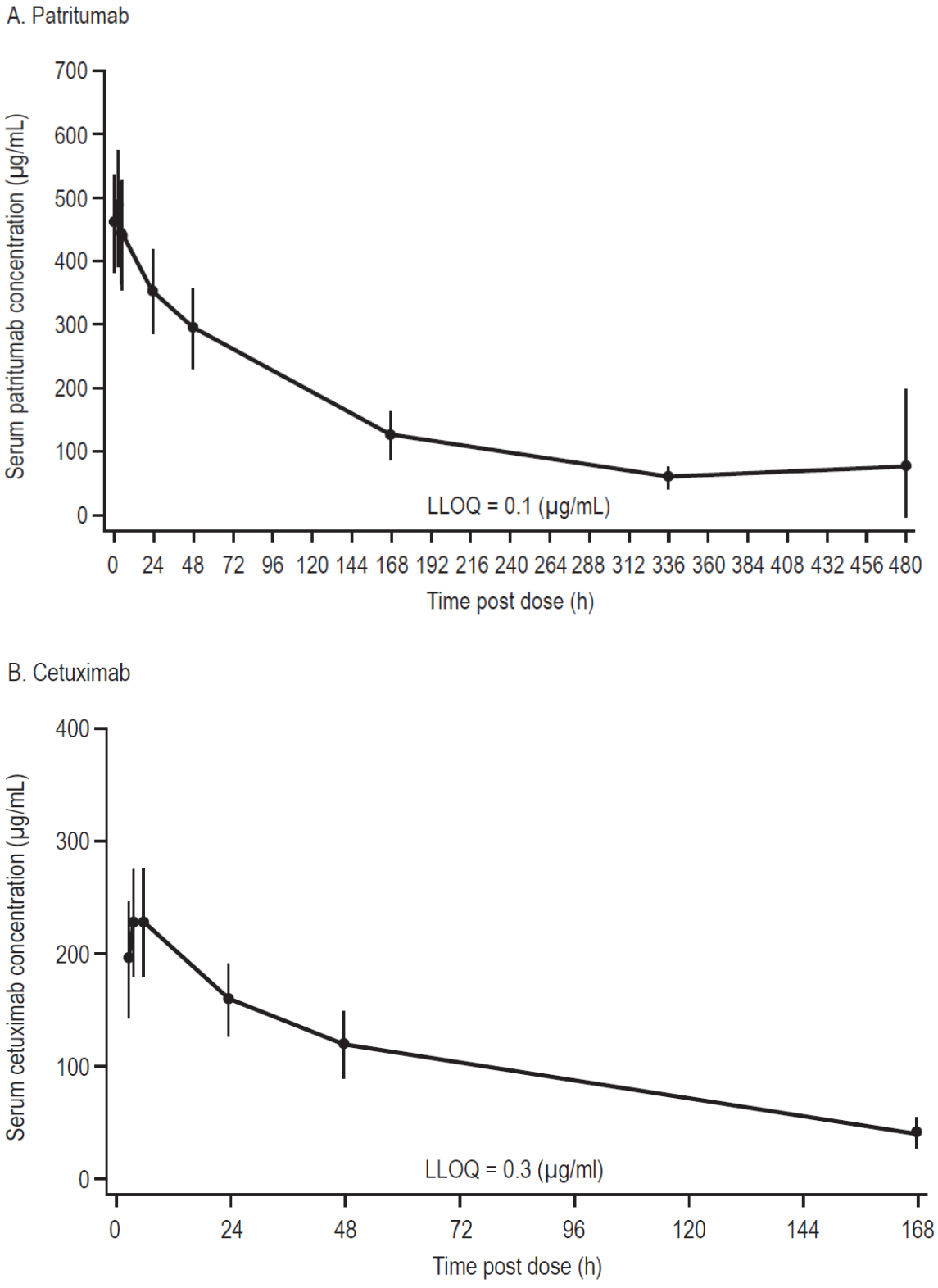

A. Patritumab
Serum patritumab concentration (µg/mL)
700
600
500
400
300
200
100
0
LLOQ = 0.1 (µg/mL)
0 24 48 72 96 120 144 168 192 216 240 264 288 312 336 360 384 408 432 456 480
Time post dose (h)
B. Cetuximab
Serum cetuximab concentration (µg/mL)
400
300
200
100
0
LLOQ = 0.3 (µg/ml)
0 24 48 72 96 120 144 168
Time post dose (h)

Figure 2.

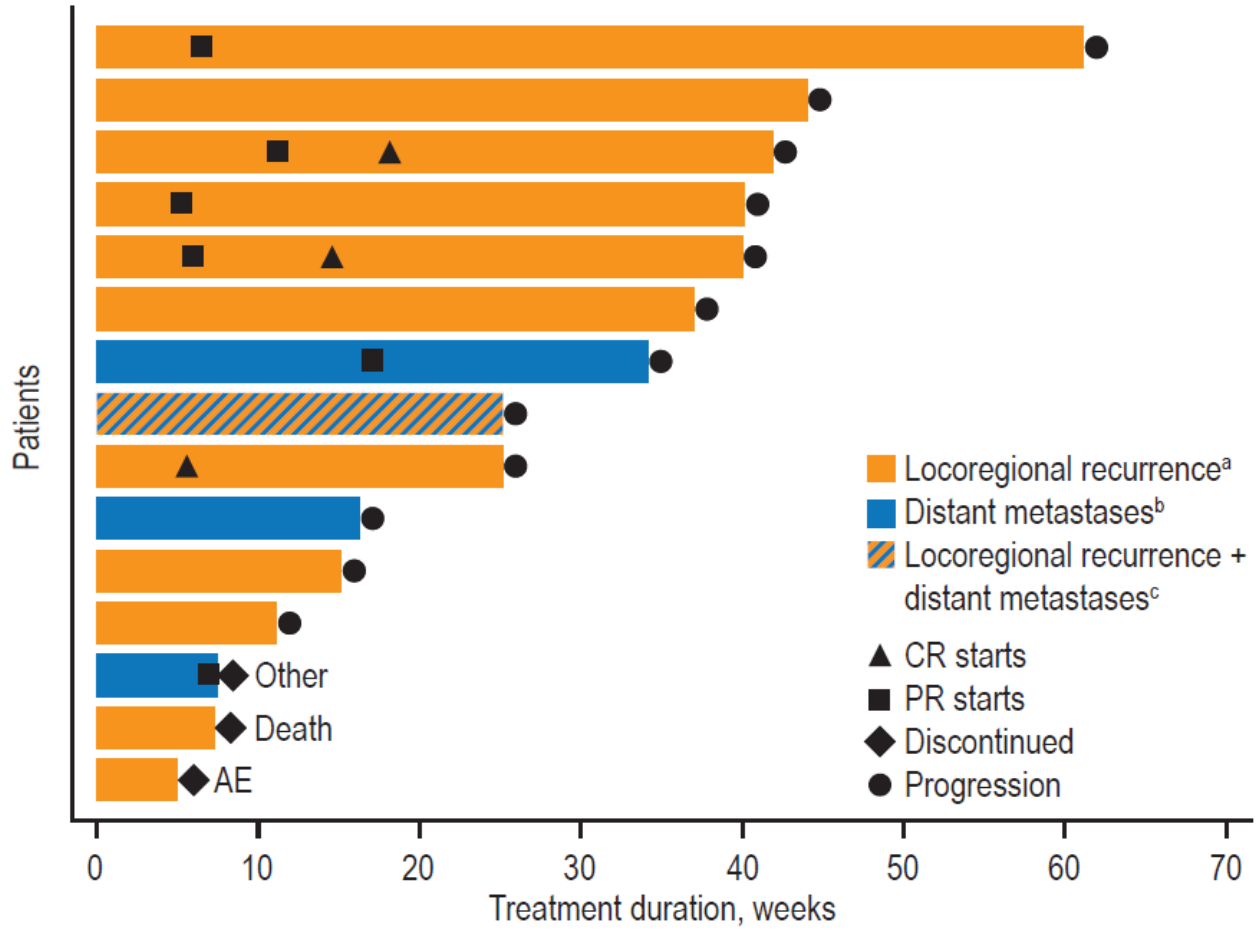
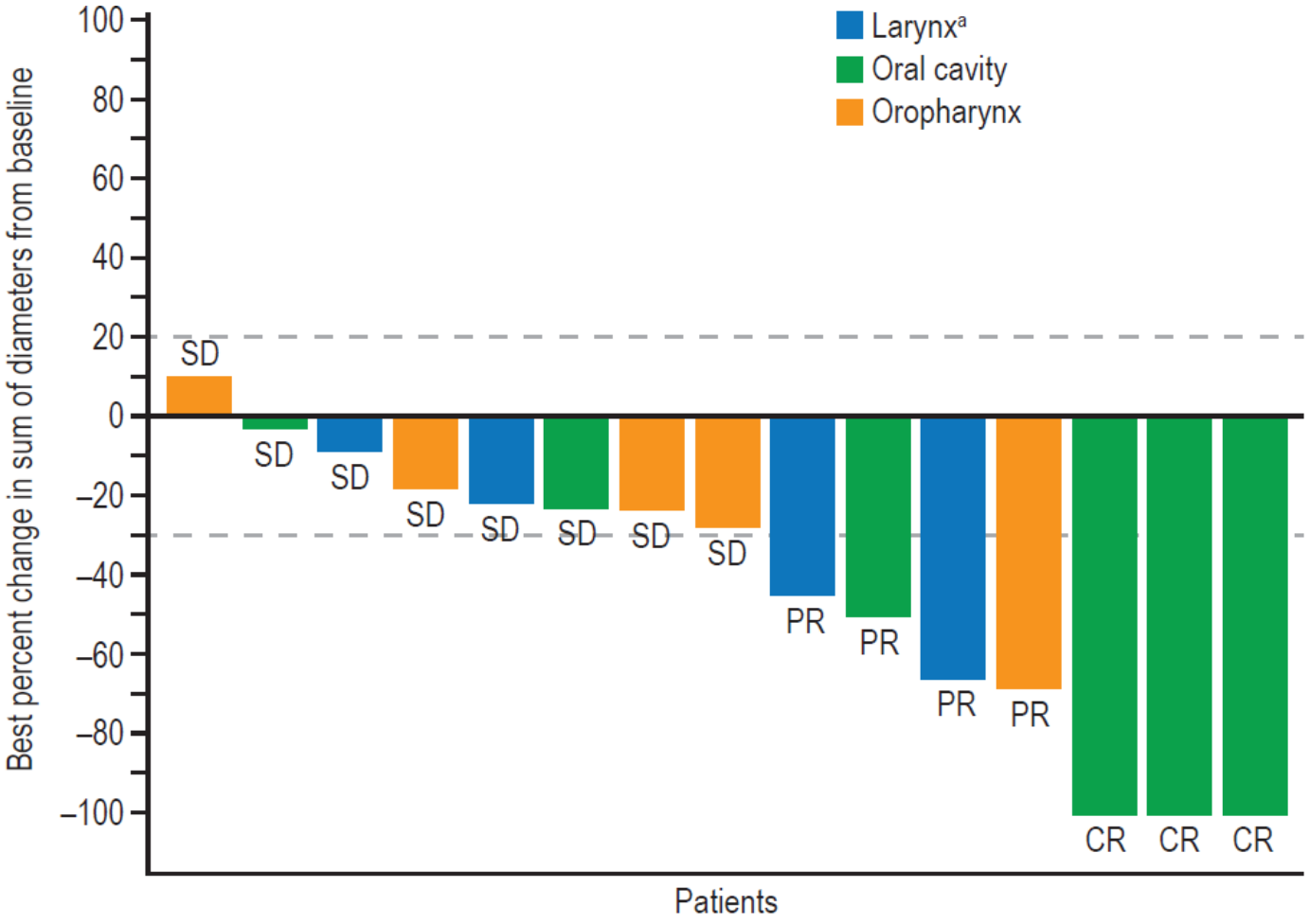

Patients
Other
Death
AE
Locoregional recurrence[a]
Distant metastases[b]
Locoregional recurrence + distant metastases[c]
CR starts
PR starts
Discontinued
Progression
0
10
20
30
40
50
60
70
Treatment duration, weeks

Figure 3.


Larynx[a]
Oral cavity
Oropharynx
Best percent change in sum of diameters from baseline
100
80
60
40
20
0
–20
–40
–60
–80
–100
SD
SD
SD
SD
SD
SD
SD
SD
PR
PR
PR
PR
CR
CR
CR
Patients

Supplementary Tables and Figures

Supplementary Table S1. Schedule of assessments

Assessment	Screening (≤21 Days of First Study Dose)	Cycle 1 (Weeks 1–3) Day 1	Cycle 1 (Weeks 1–3) Days 2, 3, 8, 15	Additional Cycles[a] (Day 1)	Every 6 weeks	End of Study (21 Days After Last Dose)	40 Days After Last Dose
Informed consent; medical history; inclusion/exclusion criteria	√						
Pregnancy test[b]	√					√	
Tumor tissue	√						
Physical exam	√	Predose	Days 8, 15	√		√	
Vital signs	√	Predose; End of infusion	Days 8, 15	√		√	
ECOG	√	Predose	Days 8, 15	√*		√	
ECG (12-lead)	√					√	

Prior/concomitant medications[c]	√	Predose; End of infusion	Days 8, 15	√		√	
CBC differential and platelets[d]	√	Predose*	Days 8*, 15*	√*		√	
Serum chemistry	√	Predose*	Days 8*, 15*	√*		√	
Urinalysis	√					√	
ECHO or MUGA[e]	√			√*		√	
AEs[f]	√	Predose; End of infusion	Days 8, 15	√		√	√
PK [g,h]		Predose*; End of infusion	Days 2, 3, 8, 15	√		√	
HAHA[h]		Predose*		√		√	
Pharmacogenomics[i]		Predose*					
Tumor assessment[j]	√				√	√	

*Assessment ≤3 business days prior to dosing.

[a]Assessments and laboratory tests occurred prior to dosing.

[b]Pregnancy test must have been confirmed negative prior to dosing.

[c]Prior medications were recorded at screening and concomitant medications were recorded prior to dosing.

[d]CBC differential and platelet results were available prior to dosing.

[e]ECHO or MUGA assessment were performed at screening and predose on day 1 of cycle 2 and additional cycles, and during the course of the study if clinically indicated and recommended by the investigator.

[f]AEs were assessed each day when infusions were given.

[g]Serum PK samples for patritumab and cetuximab concentrations were collected at cycle 1 day 1 at preinfusion, end of infusion (patritumab only), 3 hours (patritumab; cetuximab PK was collected at the end of infusion), 4 hours, 6 hours, preinfusion day 8, preinfusion day 15 (patritumab only), and preinfusion day 21 (patritumab only) relative to the start of patritumab infusion. Cetuximab PK data was available following a report of a DLT.

[h]Serum samples for patritumab PK and HAHA were collected at preinfusion at cycles 1–3 and at end-of-study visit. If patients were positive for HAHA, they would be followed every 3 months for up to 1 year.

[i]Pharmacogenetic sampling was optional; informed consent was obtained before obtaining samples.

[j]Tumor measurements were assessed per RECIST Version 1.1. Baseline scan as part of eligibility could have been performed ≤14 days prior to first dose of study drugs. Tumor assessments were performed at the end of every 2 cycles (every 6 weeks) prior to the start of the next cycle. For end-of-study visit if not performed within the past 6 weeks.

Abbreviations: AEs, adverse events; CBC, complete blood chemistry (differential and platelets); ECHO, echocardiogram; EOS, end of study; HAHA, human anti-human antibody; MUGA, multigated acquisition scan; PK, pharmacokinetics.

Supplementary Table S2. Patient disposition

Patients	***n***
Screened	17
Screen failure	2
Death during screening	1
Did not meet inclusion criteria	1
Enrolled	15
Enrolled Analysis Set (safety; DLT; PK)	15
Treatment status	
Ongoing	0
Discontinued	15
Primary reason for discontinuation	
Completed, per protocol	9
Adverse event	1
Progressive disease, per RECIST	3
Death[a]	1[a]
Other[b]	1[b]
Entered extension treatment	9
Ongoing	0
Discontinued	9
Primary reason for discontinuation	
Progressive disease, per RECIST	7
Clinical progression	2

[a]One death (due to cardiac arrest) occurred during the study and was considered related to cetuximab and carboplatin.

[b]Work-related injury.

Abbreviations: DLT, dose limiting toxicity; PK, pharmacokinetics; RECIST; Response Evaluation Criteria In Solid Tumors.

Supplementary Table S3. Study drug exposure (safety population)

	Patritumab (*n*=15)	Cetuximab (*n*=15)	Carboplatin (*n*=7)	Cisplatin (*n*=7)
Treatment duration, median (range)				
Weeks	26.1 (5.9–62.0)	26.0 (5.9–62.0)	13.5 (5.9–22.0)	18.9 (11.1–25.0)
Cycles	8.7 (2.0–20.7)	8.7 (2.0–20.7)	4.5 (2.0–7.3)	6.3 (3.7–8.3)
Cumulative dose received per patient, mg				
Mean (SD)	6243.2 (3,496.0)	10,892.2 (6,610.5)	2654.0 (1,041.4)	855.8 (261.6)
Median (range)	5339.7 (1,710.0–11,259.0)	10,442.5 (2,481–22,873.9)	2695.0 (830.0–4,150.0)	960.0 (520.4–1,136.5)

Supplementary Table S4. PK for patritumab and cetuximab loading doses (Cycle 1)

PK parameter	Patritumab	Cetuximab
	18-mg/kg loading dose (*N*=15)	**400-mg/m^2 loading dose (*N*=15)**
$AUC_{0–21d}$, µg·day/mL, mean (SD)	2,619 (560)	706 (161)
$AUC_{0–inf}$, µg·day/mL, mean (SD)	2,957 (720)	800 (259)
C_{max}, µg/mL, mean (SD)	499.9 (90.4)	246.7 (48.3)
T_{max}, hours, median (range)	2.8 (1.0–6.1)	2.6 (10.0–5.0)
$T_{1/2}$, days, mean (SD)	6.6 (2.1)	2.8 (0.4)

Abbreviations: $AUC_{0–21d}$, area under the concentration-time curve from day 0–21; $AUC_{0–inf}$, AUC from day 0–infinity; C_{max}, maximum concentration; $T_{1/2}$, clearance half-life; T_{max}, time to maximum concentration.

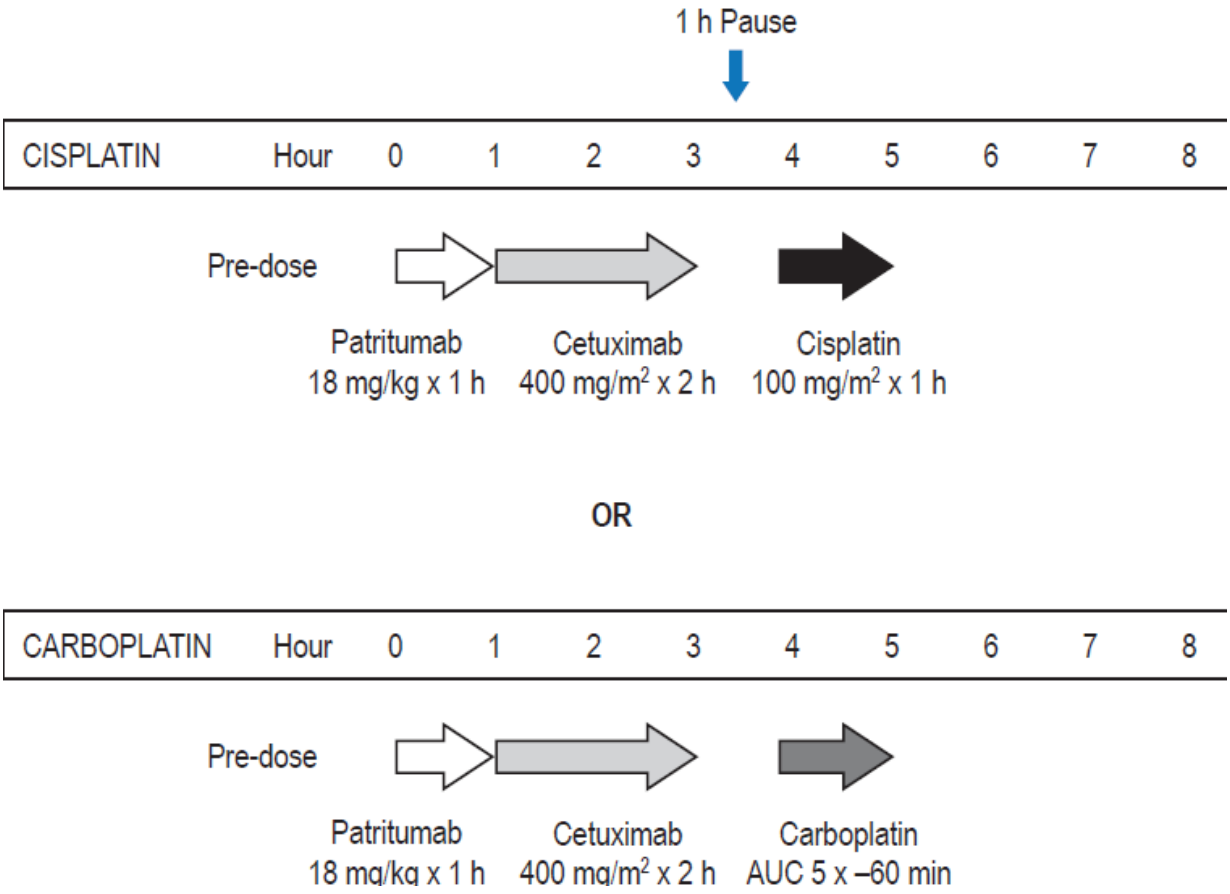
PK, pharmacokinetics; SD, standard deviation.

Supplementary Table S5. Efficacy results

Efficacy parameter	***N*=15**
Tumor response rate (CR + PR), %	47
Tumor response, *n* (%)	
CR	3 (20)
PR	4 (27)
SD	8 (53)
PD	0
Median PFS (95% CI), months	7.9 (3.7–9.7)
PFS rate over time (95% CI), %	
3 months	85.7 (53.9–96.2)
6 months	54.6 (25.4–76.5)
9 months	39.0 (14.3–63.3)
12 months	7.8 (0.5–29.5)
Median OS (range), months	13.5 (2.1–23.1)

Abbreviations: CR, complete response rate; OS, overall survival; PD, progressive disease; PR, partial response; SD, stable disease.

Supplementary Fig. S1. Phase Ib treatment administration and dosing sequence for day 1 of each cycle (loading doses only)[a]



[a]Patritumab: loading dose = 18 mg/kg; maintenance dose = 9 mg/kg. Cetuximab: loading dose = 400 mg/m^2; maintenance dose = 250 mg/m^2. AUC, area under the curve; h, hour.

Supplementary Fig. S2. Kaplan-Meier plots of **A**, Progression-free survival (PFS) and **B**, Overall survival (OS).