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PARTNER: An open-label, randomized, phase 2 study of docetaxel/cisplatin chemotherapy with or without panitumumab as first-line treatment for recurrent or metastatic squamous cell carcinoma of the head and neck

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ABSTRACT

Objective: This phase 2 estimation study evaluated docetaxel/cisplatin with/without panitumumab, an anti–epidermal growth factor receptor monoclonal antibody, as first-line therapy for recurrent/metastatic squamous cell carcinoma of the head and neck (SCCHN).

Patients and methods: Randomized patients received docetaxel/cisplatin (75 mg/m^2 each) with/without panitumumab (9 mg/kg) in 21-day cycles. Patients randomized to panitumumab + chemotherapy could continue panitumumab monotherapy after completing six chemotherapy cycles without progression; patients randomized to chemotherapy alone could receive second-line panitumumab after progression. Progression-free survival (PFS) was the primary endpoint. Secondary endpoints included overall survival (OS), overall response rate (ORR), time to response (TTR), duration of response (DOR), and safety. A protocol amendment limited enrollment to patients <70 years owing to excess toxicity in older patients and added mandatory pegfilgrastim/filgrastim support. Outcomes were also analyzed by human papillomavirus status.

Results: 103 of the 113 enrolled patients were evaluable and randomized to receive ⩾1 dose of first-line treatment. Median PFS for panitumumab + chemotherapy was 6.9 (95% CI = 4.7–8.3) months versus 5.5 (95% CI = 4.1–6.8) months for chemotherapy alone (hazard ratio [HR] = 0.629; 95% CI = 0.395–1.002; P = 0.048). ORR for panitumumab + chemotherapy was 44% (95% CI = 31–58%) versus 37% (95% CI = 24–51%) for chemotherapy alone (odds ratio [OR] = 1.37; 95% CI = 0.57–3.33). Median OS for panitumumab + chemotherapy was 12.9 (95% CI = 9.4–18.5) months versus 13.8 (95% CI = 11.8–22.9) months for chemotherapy alone (HR = 1.103; 95% CI = 0.709–1.717). Median TTR for panitumumab + chemotherapy treatment was 6.9 weeks versus 11.0 weeks for chemotherapy alone. Median DOR was 8.0 (95% CI = 5.7–11.1) months with panitumumab + chemotherapy versus 5.1 (95% CI = 4.4–7.2) months with chemotherapy alone. Grade 3/4 adverse event incidence was 73% with panitumumab + chemotherapy versus 56% with chemotherapy alone. 41% and 55% of patients in the panitumumab + chemotherapy and chemotherapy-alone arms, respectively, received panitumumab monotherapy.

Conclusion: The addition of panitumumab to docetaxel/cisplatin may improve PFS in recurrent/metastatic SCCHN and has the potential to improve outcomes in these fully, or mostly, active patients.

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Introduction

Approximately 686,330 cases of head and neck cancer (including nasopharyngeal carcinoma) occurred worldwide in 2012 [1], and an estimated 48,330 new cases will occur in the United States in 2016 [2]. Ninety percent of these tumors were squamous cell carcinoma of the head and neck (SCCHN) [3]. Approximately 12% of SCCHN cases diagnosed present with distant metastases [4], and ⩾50% of patients with locally advanced disease develop incurable relapse [5]. Notably, recent evidence indicated human papillomavirus (HPV)-positive and HPV-negative SCCHN are clinically and biologically distinct in the primary disease setting [6,7]. HPV-positive status has been associated with increased disease-free survival and overall survival (OS) in patients with oropharyngeal cancer [8,9].

Locoregionally, recurrent and/or metastatic SCCHN is usually treated with systemic chemotherapy [8]. Platinum-based combination regimens have activity in incurable SCCHN; however, benefits are limited and improved therapies are needed. Combination cisplatin/5-fluorouracil provides an objective response rate (ORR) of 30%, with median OS of 5–7 months [10,11]. Numerous clinical trials have shown taxanes are among the most active antitumor agents in SCCHN, with ORR reaching 40% (with paclitaxel) to 42% (with docetaxel) [12]. A phase 2 study using docetaxel/cisplatin to treat recurrent SCCHN demonstrated a median OS of 9.6 months with acceptable safety, suggesting the combination may provide an active but less toxic backbone for the addition of biologic therapies [13].

The epidermal growth factor receptor (EGFR) is an established therapeutic target in SCCHN. The addition of the anti-EGFR monoclonal antibody cetuximab to platinum-based chemotherapy/5-fluorouracil significantly prolonged median OS, progression-free survival (PFS), and ORR versus chemotherapy alone [14]. In the phase 3 SPECTRUM study, the addition of panitumumab to cisplatin/5-fluorouracil did not significantly improve OS (median, 11.1 versus 9.0 months; $P = 0.14$) versus cisplatin/5-fluorouracil alone, but did significantly improve PFS (median, 5.8 versus 4.6 months; $P < 0.004$) and ORR (36% versus 25%; $P < 0.007$). Notably, OS improvements were more pronounced in patients with HPV-negative tumors (HPV-negative, 11.7 versus 8.6 months, $P = 0.01$; HPV-positive, 11.0 versus 12.6 months, $P = 1.0$) [15]. Combination of anti-EGFR monoclonal antibodies with docetaxel/cisplatin also appears feasible; in a phase 2 study, cetuximab plus docetaxel/cisplatin led to an ORR of 44% at 12 weeks and median PFS and OS of 6.2 and 14.0 months, respectively, with manageable toxicity [16].

This multicenter, randomized, open-label, phase 2 estimation study (PARTNER; ClinicalTrials.gov, NCT00454779) evaluated the combination of docetaxel/cisplatin with panitumumab versus docetaxel/cisplatin alone as treatment for recurrent/metastatic SCCHN, as well as second-line panitumumab monotherapy for patients who did not respond to docetaxel/cisplatin treatment. The study protocol was amended to further evaluate outcomes by HPV status.

Patients and methods

Eligibility

Eligible patients (⩾18 years) had histologically/cytologically confirmed SCCHN; primary tumor of the oropharynx, oral cavity, hypopharynx, larynx, or SCCHN of unknown primary origin; disease considered incurable by surgery/radiotherapy; no prior systemic therapy for recurrent/metastatic disease; Eastern Cooperative Oncology Group (ECOG) performance status ⩽1; and one or more measurable target lesions per modified Response Evaluation Criteria In Solid Tumors (RECIST) version 1.0. Eligible patients must have completed radiotherapy as primary therapy >4 weeks before and chemotherapy >24 weeks before randomization. Patients were excluded if they had documented/symptomatic central nervous system metastases, nasopharyngeal carcinoma, history of interstitial lung disease, clinically significant cardiovascular disease, or any comorbid disease/condition that would increase toxicity risk. The protocol was amended to exclude patients ⩾70 years of age owing to the early observation of more deaths, primarily due to infectious/febrile neutropenic episodes, in this age group (see Results, Adverse Events). Institutional review boards approved study procedures at each site; patients provided signed informed consent.

Study design

Patients were randomized to receive docetaxel (75 mg/m^2) and cisplatin (75 mg/m^2) with or without panitumumab (9 mg/kg) in 21-day cycles (Fig. 1). Panitumumab doses could be withheld, reduced, or delayed because of toxicity. If panitumumab dosing was delayed, chemotherapy dosing continued as scheduled. Upon resolution of the toxicity, attempts to re-escalate the panitumumab dose to the starting dose were permitted. Chemotherapy dose reductions because of toxicity were permitted according to investigator discretion. Carboplatin (area under the curve of 5 [AUC 5] based on the Calvert formula) could be substituted for cisplatin for patients who developed grade 2 or 3 neurotoxicity, or who experienced reduced creatinine clearance (<60 mL/min). Randomization was stratified by ECOG performance status (0 versus 1) and disease status (newly diagnosed or previously treated versus recurrent). In response to the infectious/febrile neutropenic episodes identified early in the study, the protocol was amended to include mandatory pegfilgrastim/filgrastim support from cycle 1 for all patients. Docetaxel and cisplatin were administered for a maximum of six cycles. Patients randomized to panitumumab plus chemotherapy who achieved a complete response, partial response, or stable disease and completed six cycles, or who discontinued chemotherapy because of intolerability before disease progression, continued panitumumab monotherapy as part of first-line treatment. Patients randomized to receive chemotherapy alone could receive second-line panitumumab (9 mg/kg) in 21-day cycles after initial disease progression. Panitumumab monotherapy (first- or second-line) continued until progression or unacceptable toxicity. Relative dose intensity (RDI) was calculated as the ratio of actual dose intensity to planned dose intensity.

Progression-free survival was the primary endpoint. Key secondary endpoints included OS, ORR, disease control rate, duration of response (DOR), time to response (TTR), and safety. Endpoints for second-line monotherapy (ie, after failure of docetaxel/cisplatin) included PFS, OS, ORR, disease control rate, DOR, and TTR. Tumor HPV analyses were added after evidence emerged of the prognostic and potential predictive value of HPV status in SCCHN [15,17,18]. Efficacy endpoints for HPV analysis included PFS during first-line treatment, OS, ORR, disease control rate, and safety.

Assessments

For both first- and second-line treatment, radiologic imaging of the neck, chest, and other disease sites (computed tomography or magnetic resonance imaging) for tumor response assessment was performed at baseline and every 6 ± 1 weeks thereafter. Investigators evaluated tumor response per modified RECIST version 1.0 [19]. Assessments of complete or partial response were confirmed ⩾28 days after initial evaluation of response. Tumor assessments were required for patients who discontinued treatment for any reason other than progressive disease (PD) or who had not had a

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