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Cisplatin, 5-fluorouracil, and cetuximab (PFE) with or without cilengitide in recurrent/metastatic squamous cell carcinoma of the head and neck: results of the randomized phase I/II ADVANTAGE trial (phase II part)

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Background: Recurrent and/or metastatic squamous cell carcinoma of the head and neck (R/M-SCCHN) over-expresses αvβ5 integrin. Cilengitide selectively inhibits αvβ3 and αvβ5 integrins and is investigated as a treatment strategy.
Patients and methods: The phase I/II study ADVANTAGE evaluated cilengitide combined with cisplatin, 5-fluorouracil, and cetuximab (PFE) in R/M-SCCHN. The phase II part reported here was an open-label, randomized, controlled trial investigating progression-free survival (PFS). Patients received up to six cycles of PFE alone or combined with cilengitide 2000 mg once (CIL1W) or twice (CIL2W) weekly. Thereafter, patients received maintenance therapy (cilengitide arms: cilengitide plus cetuximab; PFE-alone arm: cetuximab only) until disease progression or unacceptable toxicity.
Results: One hundred and eighty-two patients were treated. Median PFS per investigator read was similar for CIL1W + PFE, CIL2W + PFE, and PFE alone (6.4, 5.6, and 5.7 months, respectively). Accordingly, median overall survival and objective response rates were not improved with cilengitide (12.4 months/47%, 10.6 months/27%, and 11.6 months/36%, respectively). No clinically meaningful safety differences were observed between groups. None of the tested biomarkers (expression of integrins, CD31, Ki-67, vascular endothelial growth factor receptor 2, vascular endothelial-cadherin, type IV collagen, epidermal growth factor receptor, or p16 for human papillomavirus) were predictive of outcome.
Conclusion: Neither of the cilengitide-containing regimens demonstrated a PFS benefit over PFE alone in R/M-SCCHN patients.
Key words: cetuximab, cilengitide, integrin inhibitor, phase I/II, platinum-based chemotherapy with 5-fluorouracil, recurrent and/or metastatic squamous cell carcinoma of the head and neck (R/M-SCCHN)

introduction

Patients with recurrent and/or metastatic squamous cell carcinoma of the head and neck (R/M-SCCHN) have a poor prognosis. Novel effective therapeutic approaches, such as targeted therapies, are needed to help improve patient outcomes.

Cetuximab, which selectively targets cells expressing epidermal growth factor receptor (EGFR), is thus far the only drug shown to improve survival when combined with cisplatin and 5-fluorouracil (5-FU) in R/M-SCCHN [1]. Adding cetuximab to platinum/5-FU as first-line treatment of R/M-SCCHN significantly improved median overall survival (OS) by 2.7 months versus chemotherapy alone, without adversely impacting patients' quality of life [1, 2].

Inhibiting multiple molecular pathways with biologic therapies is an attractive treatment strategy for cancer [3] and currently

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under investigation for R/M-SCCHN [4]. Integrins are important in cell–extracellular matrix interaction, tumor growth, angiogenesis, and metastasis, and hence are attractive targets [5, 6]. Cilengitide, an Arg-Gly-Asp-containing cyclic peptide, selectively inhibits αvβ3 and αvβ5 integrins resulting in *in vitro* and *in vivo* antitumor activity [7]. αvβ5, but not αvβ3, is overexpressed in SCCHN tissue, whereas both integrins are expressed on sprouting vessels [8]. Preclinical studies in mice bearing xenografts (A431 epidermoid carcinoma or U87MG glioblastoma cells) demonstrated a synergistic effect between cetuximab (10 mg/kg intraperitoneal weekly) and cilengitide (25 mg/kg intraperitoneal 5×/week; Huber et al., personal communication).

The phase I part of the ADVANTAGE study demonstrated cilengitide plus cisplatin, 5-FU, and cetuximab (PFE) was well tolerated in R/M-SCCHN patients. The most common cilengitide-related adverse events (AEs) included nausea, anorexia, and asthenia, but no dose-limiting or unexpected toxicities were reported with ≤2000 mg cilengitide [9]. Cilengitide 2000 mg was selected for the subsequent randomized phase II part assessing progression-free survival (PFS). Here, the results of this phase II part are reported.

patients and methods

study design and patient eligibility

The phase II part of the ADVANTAGE trial was a multicenter, open-label, randomized, controlled study investigating cilengitide 2000 mg once (CIL1W) or twice (CIL2W) weekly plus PFE versus PFE alone

(ClinicalTrials.gov NCT00705016 [EMR 200052-013]). The trial received Institutional Review Board approval.

The main inclusion criteria were: age ≥18 years; histologically or cytologically confirmed diagnosis of R/M-SCCHN not suitable for local therapy; ≥1 lesion measurable by computed tomography scan or magnetic resonance imaging; Karnofsky Performance Status (KPS) ≥70; or Eastern Cooperative Oncology Group performance status 0–1. Major exclusion criteria were: prior systemic chemotherapy (unless part of a multimodal treatment of locally advanced disease completed >6 months before study entry); prior EGFR-targeted therapy; surgery or irradiation ≤4 weeks before study entry; hormonal or other concomitant anticancer therapies; documented or symptomatic brain or leptomeningeal metastasis; and nasopharyngeal carcinoma.

All patients provided written informed consent before enrollment (October 2008 [June 2009 for Phase II part]–September 2010).

treatment

Patients were stratified according to their KPS (<80 versus ≥80) and randomized 1 : 1 : 1 to 1 of the 3 parallel treatment arms: PFE + CIL1W, PFE + CIL2W, and PFE (Figure 1). See supplementary Data, available at *Annals of Oncology* online for further details on the randomization process.

Cetuximab was given on days 1, 8, and 15 of each 3-week cycle (initial dose of 400 mg/m^2 iv over 2 h followed by 250 mg/m^2 over 1 h). In the PFE + CIL1W arm, cilengitide 500 mg was administered on days 1–4 and cilengitide 2000 mg on days 8 and 15; in the PFE + CIL2W arm, cilengitide 2000 mg was given on days 1, 4, 8, 11, 15, and 18 of every cycle. Cilengitide was administered as 1-h iv infusion starting 1 h post-cetuximab treatment. Cisplatin 100 mg/m^2 was given as 1- to 4-h iv infusion on day 1 following cilengitide treatment. In the case of cisplatin-related toxicity, patients could switch from cisplatin to carboplatin (area under the concentration–time
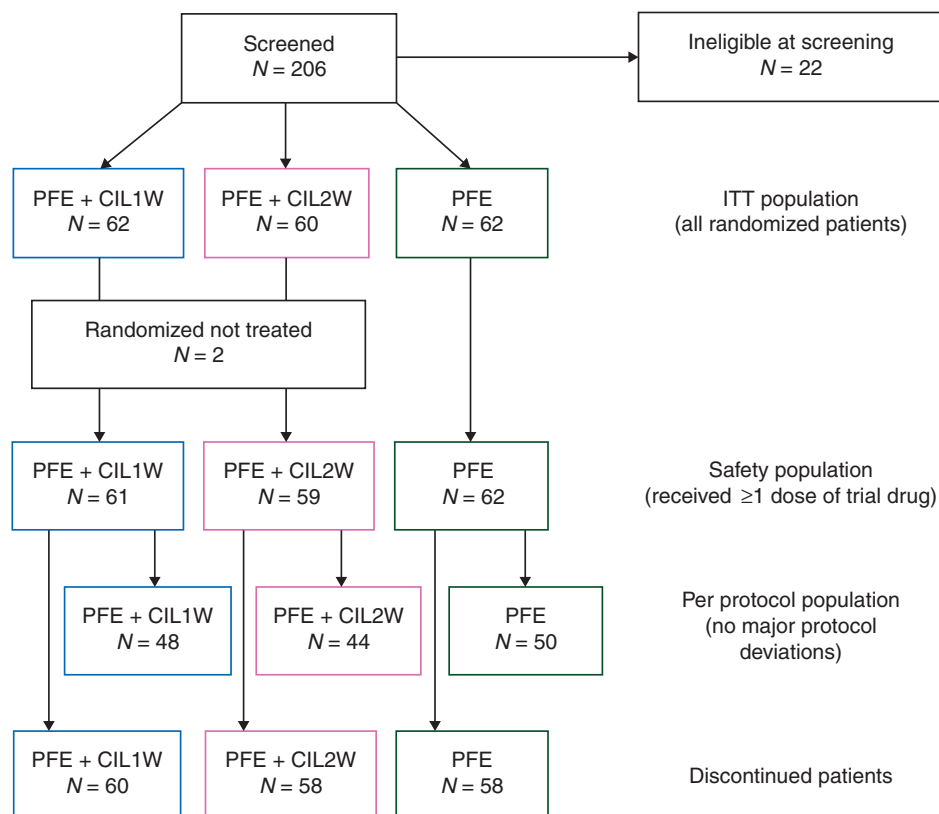

Figure 1. Disposition of patient populations. ITT, intention-to-treat; PFE, cisplatin, 5-fluorouracil, and cetuximab; PFE + CIL1W: cilengitide once weekly plus PFE; PFE + CIL2W: cilengitide twice weekly plus PFE.

curve 5). Continuous iv infusion of 5-FU 1000 mg/m^2/day was administered during days 1–4 of each cycle after cisplatin treatment.

Patients were treated for up to six cycles and then maintained with weekly cilengitide plus cetuximab (both cilengitide + PFE arms) or weekly cetuximab alone (PFE-alone arm) until disease progression (PD) or unacceptable toxicity.

study objectives

The primary objective was to evaluate PFS per investigator read. Secondary objectives were to determine OS, objective response rates (ORRs), disease control rates (DCRs), duration of response, and time-to-treatment failure (TTF); to confirm the safety profile of cilengitide plus PFE; and to determine the pharmacokinetic (PK) profile. A further objective was to identify potential biomarkers of response to the combined cilengitide/PFE treatment.

outcome measures

PFS was calculated from randomization to first observation of radiologically confirmed PD or death due to any cause. OS was calculated from randomization to death. Treatment response was assessed according to Response Evaluation Criteria in Solid Tumors version 1.0 and evaluated at baseline and every 6 weeks. The safety profile was assessed based on AEs, laboratory parameters, vital signs, physical examinations, echocardiography, and chest X-ray. The cilengitide PK profile was determined during cycle 1. Cilengitide PK parameters were calculated according to standard non-compartmental methods using the KINETICA™, version 4.1 (or higher) software. Candidate biomarkers of response were measured in formalin-fixed, paraffin-embedded (FFPE) primary tumor material using immunohisto-chemistry (IHC) and were tested for their associations with PFS, OS, and best overall response (BOR). See supplementary Data, available at *Annals of Oncology* online for details of the remaining outcome measurements.

statistical analysis

The randomized phase II selection design based on survival as described by Liu et al. [10] was used to calculate the sample size (see supplementary Data, available at *Annals of Oncology* online).

The primary end point, PFS per investigator read, and the secondary end points, OS and TTF, were analyzed using Kaplan–Meier methodology. A Cox proportional hazards model with stratification according to KPS was used to calculate hazard ratio (HR) and 95% confidence intervals (95% CIs). BOR and response duration were summarized using descriptive statistics. The association of potential biomarkers of response with clinical outcomes was tested using Cox proportional hazards modeling and multivariate logistic regression analyses.

results

patient characteristics

In total, 184 patients were randomly assigned (intention-to-treat population). Two patients left, due to symptomatic deterioration and because laboratory results disallowed treatment, respectively, and 182 received ≥1 treatment dose (safety population; Figure 1). A total of 176 patients (96%) discontinued due to PD (N = 95; 54%), AE (N = 27; 15%), death (N = 17; 10%), or other reasons (N = 37; 20%). Six patients remained on trial treatment at the data cutoff (3 September 2011; PFE + CIL1W, N = 1; PFE + CIL2W, N = 1; PFE alone, N = 4). The three treatment groups were comparable in terms of patient and disease characteristics, and previous treatment (Table 1). Median age was 57–59 years, and the majority of patients were male (82%–90%)

with a KPS score of ≥80 (89%–92%); 83%–86% of patients underwent previous anticancer treatment.

treatment exposure

Treatment duration was shorter in patients assigned to PFE + CIL2W versus PFE + CIL1W (supplementary Table S1, available at *Annals of Oncology* online). Patients received a median of 27 (range, 1–73) and 36 (range, 4–81) cilengitide infusions, respectively. However, the median cumulative cilengitide dose for patients assigned to PFE + CIL1W was lower than for the PFE + CIL2W cohort (38 000 mg [median dose intensity of 1881 mg/week] versus 54 000 mg [median dose intensity of 3579 mg/week], respectively). Throughout the study 90% (PFE + CIL1W), 86% (PFE + CIL2W) and 81% (PFE alone) of patients received cisplatin; the remainder switched to carboplatin.

survival

PFS per investigator read was not significantly different across treatment groups (median PFS: PFE + CIL1W, 6.4 months; PFE + CIL2W, 5.6 months; and PFE alone, 5.7 months; Figure 2A). Compared with PFE alone, HRs were 1.03 (95% CI 0.67–1.59; P = 0.885) for PFE + CIL1W and 1.55 (95% CI 0.99–2.43; P = 0.054) for PFE + CIL2W. A pre-specified sensitivity analysis (i.e. per independent read) showed a median PFS of 5.6 months in all cohorts (Figure 2B). HRs were 1.15 (95% CI 0.74–1.79; P = 0.528) for PFE + CIL1W, and 1.18 (95% CI 0.73–1.90; P = 0.501) for PFE + CIL2W versus PFE alone.

OS was not significantly different across treatment arms. Median OS was 11.6 months (PFE alone), 12.4 months (PFE + CIL1W; HR versus PFE alone: 0.94 [95% CI 0.61–1.47]; P = 0.800), and 10.6 months (PFE + CIL2W; HR versus PFE alone: 1.04 [95% CI 0.66–1.63]; P = 0.878) (Figure 3).

response to treatment

Objective responses per investigator read were as follows: PFE + CIL1W, 47% of patients; PFE + CIL2W, 27%; PFE alone, 36% (supplementary Table S2, available at *Annals of Oncology* online). The odds ratio (OR) for the best cilengitide group (PFE + CIL1W) versus PFE alone was 1.595 (95% CI 0.776–3.276; P = 0.205). ORR per independent read was 42%, 33%, and 32% in the PFE + CIL1W, PFE + CIL2W, and PFE-alone arms, respectively (supplementary Table S2, available at *Annals of Oncology* online). OR for the best cilengitide group (PFE + CIL1W) versus PFE alone was 1.516 (95% CI 0.732–3.141; P = 0.261). DCRs were similar across the three cohorts (supplementary Table S2, available at *Annals of Oncology* online).

A significantly shorter median response duration was observed for PFE + CIL2W (4.1 months) versus PFE alone (6.4 months; HR versus PFE alone: 2.60 [95% CI 1.30–5.21]; P = 0.007) as assessed per investigator read. This had borderline significance in the sensitivity analysis per independent read; median duration of response was 3.9 and 5.0 months with PFE + CIL2W and PFE alone, respectively (HR versus PFE alone: 1.92 [95% CI 0.99–3.74]; P = 0.053).

Median TTF per investigator read was 4.3 months for PFE alone, 5.6 months for PFE + CIL1W (HR 1.23 [95% CI 0.84–1.81]; P = 0.294 versus PFE alone), and 4.5 months for

PFE + CIL2W (HR 1.73 [95% CI 1.16–2.57]; $P = 0.007$ versus PFE alone). No sensitivity analysis was carried out for TTF.

follow-up anticancer treatment

Patients in the PFE + CIL1W and PFE + CIL2W groups received more follow-up anticancer therapy than in the PFE-alone group (47% versus 47% versus 32%, respectively); therapy consisted mostly of chemotherapy (40%, 40%, and 29%, respectively), but also comprised cetuximab (11%, 15%, and 8.1%, respectively). Patients treated with PFE + CIL2W underwent more frequent local treatment as follow-up therapy (20% [5.0% surgery and 15% radiotherapy]) than those in the PFE + CIL1W (11% [1.6% surgery and 9.7% radiotherapy]) and PFE-alone groups (3.2% radiotherapy).

pharmacokinetics

The limited data available for the PFE + CIL1W and PFE + CIL2W groups meant that only a subset of PK evaluations was carried out (supplementary Table S3, available at *Annals of Oncology* online). Maximum plasma concentration was similar on days 1 and 4 for both cilengitide groups with exposure higher on day 4 compared with day 1—a difference more prominently observed with PFE + CIL1W. However, the results were within the range of data variability, and no clinically

relevant influence of the different cilengitide dosing on cetuximab exposure was observed.

biomarkers and clinical outcome

In total, 177 (97%) patients had FFPE primary tumor samples available for biomarker assessments. IHC-based expression of integrins ($\alpha v\beta 3$, $\alpha v\beta 5$, αv, $\alpha v\beta 6$, $\alpha v\beta 8$, and $\beta 3$), CD31, Ki-67, vascular endothelial growth factor receptor 2 (VEGFR2), vascular endothelial (VE-) cadherin, type IV collagen, human papillomavirus (HPV) infection status, and EGFR were evaluated as candidate biomarkers. None could be identified as a predictive biomarker of PFS, OS, or BOR.

HPV-positive tumors, based on human cyclin-dependent kinase inhibitor 2A (p16) expression, were found in 25 (10%) patients. In 11 p16-positive tumors, the primary tumor location at first diagnosis was the oropharynx (44%; larynx: $N = 8$ [32%], hypopharynx: $N = 4$ [16%], and oral cavity and paranasal sinuses/nasal cavity $N = 1$ each [4%]).

safety

AEs were experienced in 181 patients and were considered related to cilengitide, cetuximab, or chemotherapy treatment of ≥95% of patients in each cohort (supplementary Table S4, available at *Annals of Oncology* online). Serious AEs were reported in >67% of patients across treatment arms. In each group, >90% of

Table 1. Patient demographics and baseline disease characteristics (ITT population)

Characteristics	PFE + CIL1W ($N = 62$)	PFE + CIL2W ($N = 60$)	PFE ($N = 62$)
Median age, years (range)	58 (37–79)	57 (35–73)	59 (33–75)
Male/female, %	87/13	82/18	90/10
KPS ≥80, n (%)	55 (89)	54 (90)	57 (92)
Extent of disease at study entry			
No. of patients (missing)	60 (2)	59 (1)	62 (0)
Locoregional recurrence only, n (%)[a]	30 (50)	32 (54)	31 (50)
Metastatic, with/without locoregional recurrence, n (%)[a]	30 (50)	27 (46)	31 (50)
Primary tumor site			
No. of patients (missing)	62 (0)	60 (0)	62 (0)
Oropharynx, n (%)[a]	25 (40)	23 (38)	21 (34)
Hypopharynx, n (%)[a]	10 (16)	14 (23)	14 (23)
Larynx, n (%)[a]	14 (23)	15 (25)	13 (21)
Oral cavity, n (%)[a]	11 (18)	6 (10)	11 (18)
Other, including non-classifiable, n (%)[a]	2 (3)	2 (3)	3 (5)
Primary tumor grade			
No. of patients (missing)	57 (5)	58 (2)	57 (5)
Well or moderately differentiated, n (%)[a]	46 (81)	39 (67)	35 (61)
Poorly differentiated, n (%)[a]	11 (19)	19 (33)	22 (39)
Any previous anticancer treatment, n (%)	53 (86)	50 (83)	52 (84)
Previous treatment of SCCHN, n (%)			
Neoadjuvant chemotherapy	8 (13)	2 (3)	6 (10)
Radiochemotherapy	26 (42)	22 (37)	17 (27)
Previous Pt-containing SCCHN therapy, n (%)	33 (53)	19 (32)	19 (31)

CIL1W, cilengitide once weekly; CIL2W, cilengitide twice weekly; ITT, intention-to-treat; KPS, Karnofsky Performance Status; PFE, cisplatin, 5-fluorouracil, and cetuximab; Pt, platinum; SCCHN, squamous cell carcinoma of the head and neck.
[a]Percentages were calculated based on the total number of patients with available information.
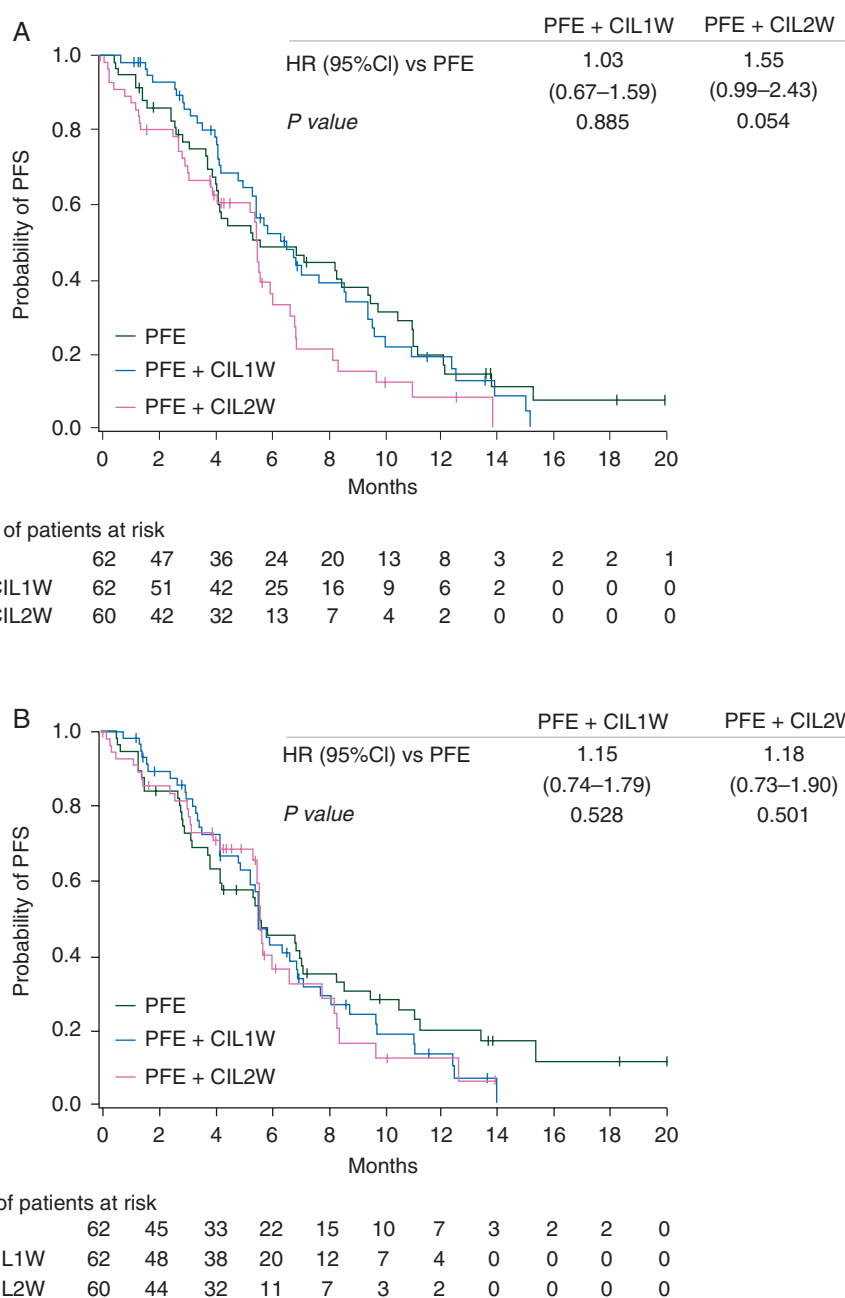
A

	PFE + CIL1W	PFE + CIL2W
HR (95%CI) vs PFE	1.03 (0.67–1.59)	1.55 (0.99–2.43)
P value	0.885	0.054

Number of patients at risk

PFE	62	47	36	24	20	13	8	3	2	2	1
PFE + CIL1W	62	51	42	25	16	9	6	2	0	0	0
PFE + CIL2W	60	42	32	13	7	4	2	0	0	0	0

B

	PFE + CIL1W	PFE + CIL2W
HR (95%CI) vs PFE	1.15 (0.74–1.79)	1.18 (0.73–1.90)
P value	0.528	0.501

Number of patients at risk

PFE	62	45	33	22	15	10	7	3	2	2	0
PFE + CIL1W	62	48	38	20	12	7	4	0	0	0	0
PFE + CIL2W	60	44	32	11	7	3	2	0	0	0	0

Figure 2. Progression-free survival in the ITT population per investigator read (A) and per independent read (B: sensitivity analysis). CI, confidence interval; CIL1W, cilengitide once weekly; CIL2W, cilengitide twice weekly; HR, hazard ratio; ITT, intention-to-treat; PFE, cisplatin, 5-fluorouracil, and cetuximab; PFS, progression-free survival.
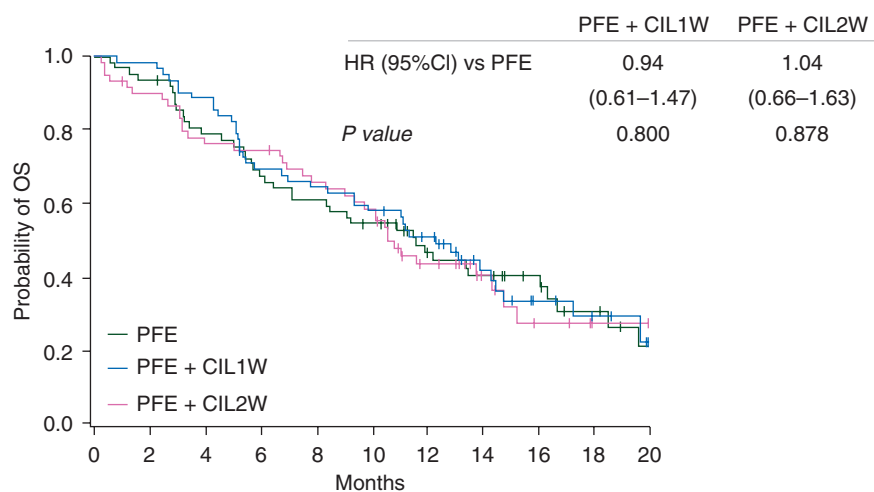
patients experienced grade 3/4 AEs, most commonly (≥15%) neutropenia, hypokalemia, leukopenia, stomatitis, fatigue, and anemia (Table 2). No clinically meaningful safety differences were noted between treatment arms.

Given cilengitide's mode of action, potential antiangiogenesis-related AEs were anticipated. Grade 3/4 thromboembolic events were experienced in 10 (PFE + CIL1W), 6 (PFE + CIL2W), and 6 (PFE alone) patients, which were within the expected range for patients undergoing chemotherapy. Grade 3/4 hemorrhages were observed at low rates overall, with a higher number with PFE alone ($N = 5$ versus PFE + CIL1W: $N = 1$, and PFE + CIL2W:

$N = 1$). Overall, AEs related to any of the study treatments led to death in seven patients (PFE + CIL1W: $N = 2$; PFE + CIL2W: $N = 2$; PFE-alone: $N = 3$); the causes of treatment-related deaths were general disorders ($N = 3$), infections and infestations ($N = 3$), and gastrointestinal disorders ($N = 1$).

discussion

This study suggests that the combination of cilengitide and PFE offered no efficacy benefits compared with PFE alone in R/M-SCCHN patients. Neither of the cilengitide-containing regimens

Figure 3. Overall survival (ITT population). CI, confidence interval; CIL1W, cilengitide once weekly; CIL2W, cilengitide twice weekly; HR, hazard ratio; ITT, intention-to-treat; OS, overall survival; PFE, cisplatin, 5-fluorouracil, and cetuximab.

Table 2. Most common grade 3/4 AEs[a] observed in at least 15% of patients (safety population)

Grade 3/4 AE[a], n (%)	PFE + CIL1W (N = 61)	PFE + CIL2W (N = 59)	PFE (N = 62)
Neutropenia	17 (28)	22 (37)	24 (39)
Hypokalemia	7 (12)	11 (19)	10 (16)
Leukopenia	7 (12)	14 (24)	7 (11)
Stomatitis	9 (15)	8 (14)	10 (16)
Fatigue	4 (7)	10 (17)	10 (16)
Anemia	5 (8)	8 (14)	9 (15)

AE, adverse event; CIL1W, cilengitide once weekly; CIL2W, cilengitide twice weekly; PFE, cisplatin, 5-fluorouracil, and cetuximab.
[a]According to National Cancer Institute Common Terminology Criteria for AEs (NCI CTC).

demonstrated that a PFS benefit versus PFE alone and OS, OR, and disease control outcomes were similar across the three cohorts. There was a trend to earlier progression in the CIL2W arm, but this did not translate into poorer survival. The reason for this observation is unclear. Baseline patient and disease characteristics were comparable across the three cohorts as were the observed AEs. Different interpretations between investigators and external reviewers, a more frequent visit schedule in the CIL2W arm, and differences in follow-up anticancer treatment may all have played a role, but these potential reasons are merely speculative.

Data from the PFE-alone group of this study were consistent with the published data from the EXTREME trial, which compared PFE with platinum/5-FU alone [1]. The EXTREME trial was conducted in the same setting as the present study and showed a significant OS increase with the addition of cetuximab to standard doses of platinum/5-FU chemotherapy. This was the first notable demonstration of a survival benefit since the introduction of cisplatin for SCCHN treatment [1].

The importance of cetuximab in the treatment of R/M-SCCHN is now acknowledged and new therapeutic strategies combining different EGFR-inhibitors, and/or simultaneous targeting of multiple pathways, are gaining recognition [3]. However, the observed synergistic effect between cetuximab and cilengitide in vitro (Huber et al. personal communication) was not confirmed in the present trial. Nevertheless, as SCCHN tissue does not overexpress $\alpha v \beta 3$, one of cilengitide's target integrins [8], these results should not be extrapolated to tumors expressing both $\alpha v \beta 3$ and $\alpha v \beta 5$. Phase I/II trials showed potential cilengitide activity as single-agent therapy in recurrent glioblastoma multiforme [11], and as concomitant and adjuvant therapy with standard chemoradiotherapy in newly diagnosed glioblastoma multiforme [12, 13].

The addition of new compounds to standard regimens for SCCHN patients with recurrent/metastatic disease may be insufficient to improve outcomes, even if preclinical data suggest potential utility. Also, most of these patients may not be eligible for combination treatment which is more aggressive than the current standard. Moving forward, biomarker-driven rationales/approaches are likely to gain more significance. In the present study, none of the tested biomarkers were found to be predictive of outcome. The low incidence of HPV-positive tumors, assessed by p16 IHC on primary tumor material, was consistent with recently reported data of the European-based EXTREME trial, where only ~10% of the evaluable patients had tumors expressing p16 [14]. A higher rate of patients with p16-positive tumors (22%) was observed in the global SPECTRUM study (randomized phase III trial comparing PF + panitumumab versus PF alone as first-line treatment of R/M-SCCHN

patients) [15]. This is most likely a consequence of the geographical differences in the trials and less likely the use of a non-standardized IHC cutoff point in SPECTRUM, as alternative cutoffs for positivity (between 10% and 70%) did not change the outcome in that study. However, the reliability of p16 to indicate HPV status is unclear outside of oropharyngeal SCCHN [16], so this conjecture may have limited relevance.

No safety concerns were identified in the present study with either of the cilengitide-containing regimens; in particular, no increased rates of angiogenesis-related AEs were reported compared with PFE alone. This confirms the safety findings of the dose-finding phase I part of the ADVANTAGE trial [9] and is consistent with the favorable tolerability to cilengitide previously observed in glioblastoma multiforme patients [11–13]. PK results concurred with outcomes from previous studies [9, 11, 12], and the cilengitide dosing did not influence the exposure to cetuximab.

In conclusion, compared with cetuximab and platinum-based chemotherapy alone, the addition of cilengitide was well tolerated, but did not result in a better outcome. Therefore, this combination cannot be recommended for further development in R/M-SCCHN patients.

disclosure

JBV, TCG, and UK served as consultants for Merck Serono and received honoraria from Merck Serono for scientific presentations at satellite symposia and advisory boards. FP and RM served as consultants or had an advisory role for Merck KGaA and received honoraria from Merck KGaA. PS received honoraria from Merck KGaA for scientific presentations and advisory boards. THB received honoraria from Merck for scientific presentations at satellite symposia and advisory boards. LI received honoraria from Merck Serono for advisory boards. UB and CH are employees of Merck KGaA. PMC received honoraria from Merck Serono for scientific presentations and advisory boards. JK, ER, JPD, and JE have no conflicts of interest to disclose.

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