Phase I/II trial of cilengitide with cetuximab, cisplatin and 5-fluorouracil in recurrent and/or metastatic squamous cell cancer of the head and neck: findings of the phase I part

JB Vermorken*1, J Guigay2, R Mesia3, JM Trigo4, U Keilholz2, A Kerber6, U Bethe6, M Picard6 and TH Brummendorf7,8

1Department of Medical Oncology, Antwerp University Hospital, Wilrijkstraat 10, Edegem 2650, Belgium; 2Department of Medicine, Head and Neck and Thoracic Medical Oncology, Gustave Roussy Institute, 39 rue Camille Desmoulins, Villejuif 94805, France; 3Department of Medical Oncology, Catalan Institute of Oncology – L’Hôpitalet, Barcelona 08097, Spain; 4Department of Oncology, Day Hospital, Malaga 29010, Spain; 5Hematology and Medical Oncology, Benjamin Franklin University, Medical Clinic III, Hindenburgdamm 30, Berlin 12200, Germany; 6Merck KGaA, Frankfurter Str. 250, Darmstadt 64293, Germany; 7Department of Oncology and Hematology, University Hospital Hamburg-Eppendorf, Martinistr. 52, Hamburg 20246, Germany; 8Department of Hematology and Oncology, University Hospital Aachen, Pouwlstraas 30, Aachen 52074, Germany

BACKGROUND: Novel therapies are needed to improve the poor prognosis of patients with recurrent and/or metastatic squamous cell cancer of the head and neck (SCCHN).

METHODS: ADVANTAGE is a phase I/II, multicentre study evaluating the integrin inhibitor cilengitide combined with cetuximab and platinum-based chemotherapy in patients with recurrent and/or metastatic SCCHN. The phase I part tested cilengitide (500, 1000 and 2000 mg) twice weekly with standard doses of cetuximab, cisplatin and 5-fluorouracil.

RESULTS: Ten patients (9 male, 1 female; median 56 years old) were included in the phase I part. No dose-limiting toxicities (DLTs: grade 3/4 toxicities in the first 3 weeks as defined per protocol) or deaths occurred. The most common adverse events (AEs) were constipation, rash, nausea, anorexia and fatigue. Cilengitide-related grade 3/4 AEs, all of which occurred after the DLT observation period, were anaemia, angiodysema, asthenia, mucosal inflammation, nausea and vomiting (one event per category). Best overall tumour response was partial response (PR) for 4 out of 10 patients and stable disease (SD) for 6 out of 10 patients across all cohorts.

CONCLUSION: Cilengitide combined with cetuximab and platinum-based chemotherapy was well tolerated. No DLTs or unexpected AEs were observed. Cilengitide 2000 mg was considered safe and was selected for the subsequent randomised phase II part assessing progression-free survival.

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Most cancers of the head and neck are located in the oral cavity, pharynx and larynx (National Comprehensive Cancer Network, 2010), and > 90% of such cancers are of squamous cell histology (Marur and Forastiere, 2008; Gregoire et al, 2010). Squamous cell cancer of the head and neck (SCCHN) accounted for 4% of all cancers worldwide in 2008, with an estimated 498 000 new cases globally in that year (Ferlay et al, 2010).

The prognosis for patients with recurrent and/or metastatic disease is extremely poor, and has remained largely unchanged in the past 30 years despite the introduction of new cytotoxic agents. The treatment goal for recurrent and/or metastatic SCCHN is symptom management and prolongation of survival (National Comprehensive Cancer Network, 2010). For those not suitable for local therapies, treatment options have been limited to systemic chemotherapy and best supportive care (Langer, 2008). With the use of platinum-based chemotherapy, median survival time is typically around 6–8 months (Langer, 2008) and the 1-year survival rate is 20–40% (Gibson et al, 2005).

The introduction of therapies targeting the epidermal growth factor receptor (EGFR) has recently improved prognosis in SCCHN patients. In a large randomised controlled trial published in 2008, the addition of cetuximab, a monoclonal antibody against EGFR, to platinum-based chemotherapy was associated with a significant improvement in overall survival (OS) and progression-free survival (PFS) and good tolerability, compared with chemotherapy alone (Vermorken et al, 2008). Median OS was 10.1 months (vs 7.4 months with chemotherapy alone, \( \text{P} = 0.04 \)) and median PFS was 5.6 months (vs 3.3 months with chemotherapy alone, \( \text{P} < 0.001 \)) (Vermorken et al, 2008). This increase in OS time of 2.7 months was a significant advance in the treatment of SCCHN, but novel approaches are urgently required to further improve survival (Bernier, 2009).
Integrins promote and regulate endothelial cell proliferation, migration, invasion, and survival in tumours, securing vascularisation and vascular remodelling in tumours (Garmy-Susini and Varner, 2008; Desrosellier and Cheresh, 2010). Squamous cell cancer of the head and neck is a highly vascularised cancer that expresses integrins: integrin \( \alpha v \beta 3 \) is primarily expressed in the endothelia of SCCHN tumours (Beer et al, 2007; Fabricius et al, 2011) while integrin \( \alpha v \beta 5 \) is primarily expressed in the tumour stroma (Fabricius et al, 2011). Cilengitide (EMD 121974, manufactured by Merck KGaA, Darmstadt, Germany) is a investigational cyclic arginine-glycine-aspartic acid (RGD) containing pentapeptide sequence that selectively inhibits the \( \alpha v \beta 3/5 \) integrins (Dechantsreiter et al, 1999). Cilengitide is the first integrin inhibitor to reach phase III clinical trials in glioblastoma, another highly vascularised cancer (Stupp et al, 2010b).

ADVANTAGE is a phase I/II trial evaluating cilengitide in combination with cetuximab, cisplatin and 5-fluorouracil (5-FU) in patients with recurrent and/or metastatic SCCHN. We report here the results of the phase I part of the ADVANTAGE study, which was designed to determine the safety and tolerability of the combination treatment at increasing doses of cilengitide.

MATERIALS AND METHODS

Study design

The ADVANTAGE trial (ClinicalTrials.gov identifier NCT00705016) is a phase I/II, multicentre study in patients with recurrent and/or metastatic SCCHN. The study is divided into two parts: a phase I part with dose escalation of cilengitide (presented here) and an open-label, randomised, controlled, phase II part, which is ongoing.

The phase I part aimed to include 9–18 patients, with 3 patients per cohort, and began in July 2008. The data cutoff point for the safety results presented here was 1 March 2010. A 3+3 design was used, consisting of a cohort-wise escalation of cilengitide in combination with cetuximab, cisplatin and 5-FU over three cohorts. Patients were observed for dose-limiting toxicities (DLTs) during the first 3-week cycle of therapy. If there were no DLTs in the three patients in cohort 1, then cohort 2 could proceed, but if one of the three patients from cohort 1 experienced a DLT, then an additional three patients were required to be evaluated in cohort 1. If a cohort was expanded to six patients in this way, the next cohort could proceed if \( \leq 2 \) of 6 patients experienced a DLT.

Patients

Inclusion criteria for the study included: (i) adults aged \( \geq 18 \) years; (ii) a histologically or cytologically confirmed diagnosis of recurrent and/or metastatic SCCHN that was not suitable for local therapy; (iii) patients with \( \geq 1 \) measurable lesion by either computerised tomography (CT) or magnetic resonance imaging (MRI); (iv) performance status \( \geq 70 \) on the Karnofsky performance status scale; and (v) 0–1 on the Eastern Cooperative Oncology Group scale.

Key exclusion criteria were (i) prior systemic chemotherapy (unless as part of multimodal treatment for locally advanced disease completed >6 months before study entry); (ii) surgery (excluding diagnostic biopsy) or irradiation \( \leq 4 \) weeks before study entry; (iii) nasopharyngeal carcinoma; (iv) active infection, uncontrolled hypertension, abnormal haematology or liver function; (v) pregnancy; (vi) other concomitant anticancer therapies or previous treatment with EGFR targeting therapy or signal transduction inhibitors; (vii) brain metastases; and (viii) known drug abuse.

The study was conducted in accordance with the Declaration of Helsinki and in compliance with Good Clinical Practice. The protocol was approved by institutional review boards, and all patients provided written informed consent.

Study intervention

The selection of cilengitide regimens in this study was based on investigations to date in patients with various cancer diagnoses. These studies demonstrated that twice weekly cilengitide up to 2400 mg m\(^{-2}\) had antitumour effects and was well tolerated (Eskens et al, 2003; Nabors et al, 2007).

Patients were given one of three cilengitide doses (500, 1000, or 2000 mg) administered intravenously (i.v.) twice a week over 1 h, in combination with standard doses of cetuximab (administered i.v. at an initial dose of 400 mg m\(^{-2}\) over 2 h, followed by weekly doses of 250 mg m\(^{-2}\) over 1 h) and chemotherapy. Chemotherapy consisted of cisplatin (100 mg m\(^{-2}\) i.v. on day 1) plus 5-FU (1000 mg m\(^{-2}\) day\(^{-1}\) continuous infusion from day 1 to 4) during the first week of each 3-week cycle. Treatment was administered for up to 6 cycles (i.e., 18 weeks), until progressive disease (PD), death, unacceptable toxicity or withdrawal of consent. Patients without progression after six cycles of therapy continued maintenance treatment with cilengitide plus cetuximab only.

Measured outcomes

The primary objective of the phase I safety run-in was to determine the safety and tolerability of cilengitide in combination with cetuximab, cisplatin and 5-FU. The study also examined activity in terms of response and disease control. Imaging studies, including CT scans or MRI of the head, neck and chest, were performed at baseline and every 6 weeks after randomisation until PD. Response was assessed according to RECIST 1.0 (Therasse et al, 2000). Disease control rate was defined as the proportion of patients whose best overall response was confirmed complete response (CR), partial response (PR) or stable disease (SD).

Safety was assessed by monitoring laboratory parameters, vital signs and adverse events (AEs) as graded according to the National Cancer Institute Common Terminology Criteria (NCI CTCAE v3.0). Treatment-related AEs were defined as AEs that the investigator deemed related to the investigational medicinal product or non-investigational medicinal product. Investigators assessed relatedness of an AE either as ‘related’ or as ‘not related’.

Definition of DLTs

The observation period for DLTs was the first 3 weeks of study treatment. During that time, DLTs were defined as follows:

- Any grade 3/4 treatment-related toxicity confirmed by the Safety Monitoring Committee to be relevant. This explicitly included:
  - Any grade 4 haematological or non-haematological toxicity if not specifically excluded (see below).
  - Any treatment-related death observed within the first 3 weeks of therapy.
- Explicitly excluded from the DLT definition were the following toxicities that are expected from treatment with cisplatin, 5-FU or cetuximab:
  - Fatigue (lethargy, malaise and asthenia – even if considered related to cilengitide).
  - Alopecia.
  - Rash of grades 3 and 4.
  - Nausea or vomiting of grades 3 and 4.
  - Neutropenia for \( \leq 5 \) days and not associated with fever.
  - Isolated lymphocytopenia or thrombocytopenia grades 3 and 4 with no clinical correlate.
  - Diarrhoea grades 3 and 4 in the absence of supportive care.
  - Single laboratory values that were out of the normal range, without clinical correlate, unlikely to be treatment-related and spontaneously resolving within 7 days.
  - Any hypersensitivity reaction (as this is independent of dose).
RESULTS

In total, 10 patients (9 male, 1 female) with a median age of 56 years (range 32–74 years) with recurrent and/or metastatic SCCHN participated in the phase I part (Table 1). Three patients were included in cohorts 1 and 2, respectively. Four patients instead of three were included in cohort 3, as two participants were screened in parallel and a request to include both in the trial was accepted. The median treatment duration of cilengitide administration was 24.4 weeks (range 12–57 weeks), and all patients completed at least three treatment cycles (Table 2). One patient completed three treatment cycles, two patients completed four treatment cycles and one patient completed five treatment cycles. Six patients completed all six treatment cycles and four out of the six patients continued maintenance treatment with cilengitide and cetuximab. The reasons for study completion/discontinuation were PD (eight patients), an AE (one patient who had elevated creatinine levels) and the investigator’s decision (one patient). Individual patient characteristics are described in Table 3.

Safety and tolerability

All patients (n = 10) experienced at least one AE during the study; however, the observed AEs were in line with the patients’ underlying disease and the known toxicities of cetuximab and the concomitant chemotherapies. No DLTs (for DLT definition, see Measured outcomes section) or deaths were reported for any patient in any cohort during the phase I component of this study. The maximum tolerated dose of cilengitide was not reached.

The most common AEs of any toxicity grade were constipation, rash, nausea, anorexia and fatigue (Table 4). Seven patients experienced an AE assessed as related to cilengitide by the investigator (one in cohort 1, three in cohort 2 and three in cohort 3). Of the most common AEs reported (in >2 patients), those assessed as related to cilengitide were nausea, anorexia, asthenia, vomiting, mucosal inflammation and dry skin (Table 4).

Grade 3/4 AEs were experienced by all 10 patients, and these were related to cilengitide in 3 patients (two in cohort 2 and one in cohort 3). Neutropenia was the most common grade 3/4 AE, but this was not assessed as related to cilengitide treatment (Table 5). Anaemia, angioedema, asthenia, mucosal inflammation, nausea and vomiting were grade 3/4 AEs that occurred after the DLT observation period and were assessed as related to cilengitide treatment. The single case of angioedema (of the throat) occurred 10 months after the start of treatment and 2 weeks after the very last administration of cetuximab and cilengitide. The investigator assigned angioedema as related to both cetuximab and cilengitide. However, the day before occurrence of angioedema, bisoprolol had been started in this patient. While anaphylactoid/anaphylactic reactions have been reported with cetuximab (Merck Serono, 2010), and angioedema has been observed with agents that have antiangiogenic properties (Bayer, 2011), the β-blocker bisoprolol is a known cause of angioedema (Duramed Pharmaceuticals, 2011). Bisoprolol was stopped the day after onset of angioedema and angioedema resolved the same day. Only one grade 4 AE occurred (a decreased neutrophil count in cohort 3) and it was not assessed by the investigator as related to cilengitide treatment.

The maximum tolerated dose of cilengitide was not reached.

Efficacy parameters

The median PFS with cilengitide in combination with cetuximab and platinum-based chemotherapy was 5.88 months (95% CI 2.96–10.15). Best overall tumour response summarised in Table 2 was PR for one and three patients in the 1000 and 2000 mg groups, respectively, and SD for three, two and one patients in the 500, 1000 and 2000 mg groups, respectively. Disease control rate (CR, PR and SD) was 100%.

DISCUSSION

This phase I part of a combined phase I/II trial defined cilengitide 2000 mg twice weekly as safe when given with cetuximab, cisplatin and 5-FU for recurrent and/or metastatic SCCHN. Observed AEs were in line with both the underlying malignant condition and the known toxicities of cetuximab and concomitant chemotherapy. The maximum tolerated cilengitide dose was not identified. No DLTs were observed.

The selection of cilengitide dose and escalation schedule was based on previous investigations in animal models and in clinical studies of patients with various types of cancers (Eskens et al, 2003). In nude mice bearing M21-L human melanoma xenografts,

Table 1 Patient demographics

| Cilengitide | Cohort 1 (n = 3) | Cohort 2 (n = 3) | Cohort 3 (n = 4) |
|------------|----------------|----------------|----------------|
| Cilengitide | 500 mg | 1000 mg | 2000 mg |
| Median (range) age, years | 56 (54–74) | 43 (32–59) | 57 (49–68) |
| Male | 3 | 2 | 4 |
| Female | 1 | 1 | - |
| ECOG performance status, n | 0 | 1 | 1 |
| 0 | 2 | 1 | 2 |
| 1 | 1 | | |

Abbreviation: ECOG = Eastern Cooperative Oncology Group.

Table 2 Cilengitide exposure and response

| Cilengitide dose | Cohort 1 (n = 3) | Cohort 2 (n = 3) | Cohort 3 (n = 4) |
|-----------------|----------------|----------------|----------------|
| Median duration of cilengitide administration (range), weeks | 23.3 (14–25) | 42.4 (35–57) | 16.3 (12–45) |
| Best overall tumour response, n | 0 | 0 | 0 |
| Complete response | 0 | 0 | 0 |
| Partial response | 0 | 1 | 3 |
| Stable disease | 3 | 2 | 1 |
| Progressive disease | 0 | 0 | 0 |
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these plasma concentrations (11–13 mg ml

metastatic solid tumours, pharmacokinetic analysis showed that

In a single-agent dose-escalation phase I study of 37 patients with

corresponding to peak plasma concentrations of 10.9–12.7 mg ml

further phase I study in 20 patients with advanced solid tumours

independent of dose and no DLTs occurred (Eskens

safety profile. The pharmacokinetic profile of cilengitide was

humans at a dose level of 120 mg m

optimal inhibition of tumour growth occurred at 10–15 mg kg

In a single-agent dose-escalation phase I study of 37 patients with metastatic solid tumours, pharmacokinetic analysis showed that these plasma concentrations (11–13 mg ml⁻¹) were achieved in humans at a dose level of 120 mg m⁻² (Eskens et al, 2003). Ten dose levels of cilengitide (30–1600 mg m⁻² i.v. twice weekly) were examined in this study and cilengitide was associated with a good safety profile. The pharmacokinetic profile of cilengitide was independent of dose and no DLTs occurred (Eskens et al, 2003). A further phase I study in 20 patients with advanced solid tumours investigated two doses of cilengitide (600 and 1200 mg m⁻²) administered i.v. twice weekly for a median number of 20 infusions per patient (Hariharan et al, 2007). No DLTs were associated with cilengitide, and it was well tolerated.

Cilengitide has previously been examined in patients with refractory brain tumours, in a phase I study of 31 paediatric patients (<21 years old) who received cilengitide at doses of 120–2400 mg m⁻² i.v. twice weekly, for up to 52 weeks (MacDonald et al, 2008). The results were similar to those of the current study, with no DLTs observed. The twice weekly dosage of 1800 mg m⁻² was recommended for the phase II part of the trial (MacDonald et al, 2008). An open-label phase I study investigated the toxicity and maximum tolerated dose of cilengitide in 51 adults with recurrent malignant glioma (Nabors et al, 2007). Based on the data from previous studies, cilengitide was administered in eight different doses from 120 to 2400 mg m⁻² i.v. twice weekly in cohorts containing six evaluable patients (Nabors et al, 2007). There was no evidence of any cilengitide-related acute toxicities and a maximum tolerated dose was not identified. Some DLTs occurred and AEs were mostly mild and the majority were not attributable to cilengitide. Cilengitide was well tolerated up to doses of 2400 mg m⁻². Several phase II trials have investigated the effects of cilengitide (500 or 2000 mg twice weekly) in patients with newly diagnosed or recurrent glioblastoma (Gilbert et al, 2007; Reardon et al, 2008; Stupp et al, 2010a). These studies found that cilengitide was well tolerated, with promising antitumour activity and no significant reproducible toxicities. The higher dose of cilengitide (2000 mg) was favourable with respect to OS and PFS and was thus recommended for subsequent trials (Nabors et al, 2007; Reardon et al, 2008; Stupp et al, 2010a).

The rationale for combining cilengitide with cetuximab and platinum-based chemotherapy was based upon preclinical data illustrating cross talk between integrins and members of the EGFR

Table 3 Patient characteristics

| ID          | Gender | Age (years) | Locoregional recurrence or metastasis of SCCHN | Localisation of metastases | Histological grading of squamous cell carcinoma | TNM stage at first diagnosis of SCCHN | Primary tumour site | ECOG performance status |
|-------------|--------|-------------|------------------------------------------------|-----------------------------|-----------------------------------------------|---------------------------------------|---------------------|------------------------|
| 02010001    | Male   | 56          | Distant metastasis                             | Liver                       | Unknown                                       | T3N2M0                                | Pharynx            | 0                      |
| 02010002    | Female | 43          | Locoregional recurrence                        | Not applicable              | Well differentiated                           | T1N0M0                                | Tongue             | 1                      |
| 02010003    | Male   | 52          | Distant metastasis                             | Liver                       | Moderately differentiated                     | T4N2M1                                | Pharynx            | 0                      |
| 03010001    | Male   | 59          | Locoregional recurrence                        | Not applicable              | Unknown                                       | T4N3M0                                | Lung                | 0                      |
| 04010001    | Male   | 74          | Distant metastasis                             | Lung                        | Poorly differentiated                         | T4N3M1                                | Larynx             | 1                      |
| 04010004    | Male   | 49          | Distant metastasis                             | Cutaneous, skeletal, lymph nodes | Poorly differentiated                         | T4N2M1                                | Pharynx            | 1                      |
| 08010001    | Male   | 32          | Distant metastasis                             | Lung, hepatic, kidney       | Poorly differentiated                         | T1N1M1                                | Tongue             | 0                      |
| 08010002    | Male   | 57          | Locoregional recurrence                        | Not applicable              | Well differentiated                           | T2N2M0                                | Tongue             | 1                      |
| 03010002    | Male   | 49          | Distant metastasis                             | Not applicable              | Unknown                                       | T4N3M1                                | Lung                | 1                      |
| 04010001    | Male   | 54          | Locoregional recurrence                        | Not applicable              | Unknown                                       | T4N3M0                                | Larynx             | 1                      |
| 04010002    | Male   | 74          | Distant metastasis                             | Lung                        | Poorly differentiated                         | T4N3M1                                | Lung                | 1                      |
| 04010004    | Male   | 49          | Distant metastasis                             | Cutaneous, skeletal, lymph nodes | Poorly differentiated                         | T4N2M1                                | Pharynx            | 1                      |
| 08010001    | Male   | 32          | Distant metastasis                             | Lung, hepatic, kidney       | Poorly differentiated                         | T1N1M1                                | Tongue             | 0                      |
| 08010002    | Male   | 57          | Locoregional recurrence                        | Not applicable              | Well differentiated                           | T2N2M0                                | Tongue             | 1                      |

Abbreviations: ECOG = Eastern Cooperative Oncology Group; SCCHN = squamous cell cancer of the head and neck; TNM = tumour node metastasis.

Table 4 Most frequent AEs (reported in >2 out of 10 patients) and most frequent AEs assessed as related to cilengitide (>2 out of 10 patients in total)

|                | Most frequent AEs related to cilengitide (n = 10 patients) |
|----------------|------------------------------------------------------------|
|                | Cohort 1 (n = 3)               | Cohort 2 (n = 3)         | Cohort 3 (n = 4)         |
| Cilengitide    | 500 mg                      | 1000 mg                   | 2000 mg                   |
| Constipation   | 8                           | 5                         | 0                         |
| Rash           | 7                           | 3                         | 0                         |
| Nausea         | 7                           | 2                         | 1                         |
| Anorexia       | 7                           | 1                         | 2                         |
| Fatigue        | 6                           | 0                         | 2                         |
| Asthenia       | 5                           | 0                         | 1                         |
| Pyrexia        | 5                           | 0                         | 2                         |
| Diarrhoea      | 5                           | 0                         | 1                         |
| Vomiting       | 5                           | 0                         | 2                         |
| Skin fissures  | 4                           | 0                         | 2                         |
| Stomatitis     | 4                           | 0                         | 1                         |
| Anaemia        | 4                           | 0                         | 1                         |
| Neutropenia    | 4                           | 0                         | 0                         |
| Mucosal inflammation | 3             | 0                         | 1                         |
| Dry skin       | 3                           | 0                         | 2                         |
| Hypokalaemia   | 3                           | 0                         | 1                         |
| Dizziness      | 3                           | 0                         | 1                         |
| Paraesthesia   | 3                           | 0                         | 1                         |

Abbreviation: AEs = adverse events. *Regardless of toxicity grade. **Any AEs, regardless of relatedness to cilengitide. Investigators assessed AEs either as ‘related’ or as ‘not related.”
family (Desgrosellier and Cheresh, 2010). Also, there is evidence that integrin inhibitors may be most effective when combined with chemotherapies (Abdollahi et al, 2005; Desgrosellier and Cheresh, 2010). Pharmacokinetic analyses are planned for the phase II part of this study, as well as pharmacodynamic and pharmacogenetic assessments.

Despite recent therapeutic advances such as cetuximab combined with platinum-based chemotherapy, which can extend survival in patients with recurrent and/or metastatic SCCHN, patients still have a poor prognosis (Vermorken et al, 2008). Cilengitide is an integrin inhibitor, with a different mode of action compared with the other therapeutic agents currently in clinical practice for the treatment of SCCHN. It is hypothesised that cilengitide will increase antitumour activity without compromising safety and tolerability. A case report describes a patient with a highly proliferative squamous cell carcinoma of the upper left jaw (Raguse et al, 2004). The patient received 600 mg m\(^{-2}\) cilengitide i.v. twice weekly in combination with 1000 mg m\(^{-2}\) gemcitabine twice weekly every 3 weeks for 5 months followed by maintenance therapy with 600 mg m\(^{-2}\) cilengitide i.v. twice weekly in a clinical setting (Raguse et al, 2004). The patient remained stable for 12 months and achieved a partial remission, demonstrating the clinical potential of cilengitide (Raguse et al, 2004).

The current findings of the phase I part of ADVANTAGE are promising since they demonstrate an acceptable tolerability profile of cilengitide and absence of DLTs in patients with recurrent and/or metastatic SCCHN. The randomised phase II part of this trial is currently investigating PFS in patients with SCCHN treated with two regimens of 2000 mg cilengitide (weekly vs twice weekly administration) combined with cetuximab, cisplatin and 5-FU, compared with cetuximab, cisplatin and 5-FU alone. On the basis of the available preclinical and clinical phase I/II data for cilengitide in recurrent malignant glioma, and the findings from this phase I part, two regimens have been selected for the phase II part of ADVANTAGE: cilengitide 500 mg four times a week (week 1) followed by 2000 mg cilengitide (weeks 2 and 3) for group A or 2000 mg cilengitide twice weekly for group B.

In conclusion, the current study investigates a combination of the integrin inhibitor cilengitide with cetuximab and platinum-based chemotherapy in patients with recurrent or metastatic SCCHN. In the phase I safety run-in, cilengitide in combination with cetuximab, cisplatin and 5-FU was well tolerated, associated with no unexpected AEs and no DLTs, and no maximum tolerated dose was identified. A dose of cilengitide 2000 mg was selected for the phase II study, which will assess PFS in a larger patient group.

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Table 5 Grade 3/4 AEs and their relatedness to cilengitide

| Cilengitide       | Cohort 1 (n = 3) | Cohort 2 (n = 3) | Cohort 3 (n = 4) |
|-------------------|-----------------|-----------------|-----------------|
|                   | 500 mg          | 1000 mg         | 2000 mg         |
| Anaemia           | 2               | 1 1b            | 1 1b            |
| Angioedema        |                 |                 | 1 1b            |
| Asthenia          |                 |                 | 1 1a            |
| Deafness          |                 |                 |                 |
| Decreased neutrophil count |             |                 |                 |
| Decreased white blood cell count |         |                 |                 |
| Dehydration       |                 |                 |                 |
| Diarrhoea         |                 |                 |                 |
| Dizziness         |                 |                 |                 |
| Fatigue           |                 |                 |                 |
| Febrile neutropenia |               |                 |                 |
| Hypertension      |                 |                 |                 |
| Hypocalcaemia     |                 |                 |                 |
| Hypokalaemia      |                 |                 |                 |
| Hypophosphataemia |                 |                 |                 |
| Lung infection    |                 |                 |                 |
| Mucosal inflammation |             |                 |                 |
| Nausea            | 1a 1a           | 1a              | 1a              |
| Neutropenia       | 1               | 2 1a            |                 |
| Pneumonia         |                 |                 |                 |
| Vomiting          | 1a              |                 |                 |

Abbreviation: AEs = adverse events. *Assessed as related to cilengitide: all of these occurred after the DLT observation period. See more detailed information on angioedema in Results section.
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