Phase II study of single-agent panitumumab in patients with incurable cutaneous squamous cell carcinoma

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Background: Although advanced cutaneous squamous cell carcinoma (CSCC) is quite common, there are few prospective trials regarding its optimal management. This study evaluated the efficacy and safety of single-agent panitumumab in the treatment of patients with CSCC not suitable for local therapy.

Patients and methods: Sixteen patients received single-agent panitumumab at a dose of 6 mg/kg repeated every 2 weeks for a minimum of three cycles and continued until progression, a maximum of nine cycles or dose-limiting toxicity. The primary end point was the best overall response rate (ORR) as assessed by Response Evaluation Criteria in Solid Tumours (RECIST version 1.1) criteria. Secondary end points included evaluation of safety, toxicity and progression-free survival (PFS).

Results: Between May 2010 and May 2012, 16 patients were recruited. Fourteen patients were male and the median age was 68 years. Fifteen patients had locoregionally advanced or recurrent disease with 14 patients receiving previous radiotherapy and 7 receiving previous cytotoxic chemotherapy. The best ORR [partial (PR) or complete response (CR)] was 31% (3/16 PR, 2/16 CR) with a further 6 of 16 patients achieving SD. The median PFS and overall survival were 8 and 11 months respectively. Grade 3 or 4 events were observed in five patients (four being skin toxicity) with one...
patient ceasing due to skin toxicity. With a median follow-up of 24 months, 10 patients died due to progressive disease, 6 are alive, one patient with no evidence of disease at the time of analysis.

**Conclusions:** Single-agent panitumumab is safe and effective in the management of patients with advanced CSCC even in a previously extensively pre-treated cohort.

**Key words:** cutaneous, squamous cell carcinoma, panitumumab

### introduction

Non-melanoma skin cancer (NMSC) is the most common malignancy worldwide and a consequence of chronic exposure to the mutagenic solar ultraviolet radiation [1]. The sun-exposed head and neck is the most common site (70%–80%) for the development of a NMSC, and populations of fair-skin individuals living in countries close to the equator and tropics are more commonly affected. Since the 1960s, the worldwide incidence of advanced cutaneous squamous cell carcinoma (CSCC), usually as a result of developing metastatic nodal disease [4]. Despite aggressive treatment with surgery and radiotherapy, a number of these patients will fail or develop incurable distant metastatic disease.

Investigation of systemic therapy for this disease has been limited to few prospective trials. Systemic therapies that have been used to treat patients with advanced CSCC include cytotoxic chemotherapy [cisplatin, 5-flourouracil (5-FU), bleomycin and doxorubicin], 13-cis-retinoic acid (13-cRA) and immunotherapy [interferon α2a (IFN-α2a)] [5–10]. Although these agents have shown activity in the metastatic setting, the toxic effects of these combinations make their use in this population, which is often elderly, limited.

The epidermal growth factor receptor (EGFR) is highly expressed in many epithelial cancers including CSCC [11, 12]. Although tumour EGFR expression correlates inversely with clinical outcome [13], the degree of over expression does not seem to correlate with the effectiveness of EGFR inhibitors and several mechanisms of resistance are under investigation [14–16]. Irrespective, inhibition of this signal transduction pathway in CSCC has been evaluated with the tyrosine kinase inhibitor, gefitinib [17] and humanised monoclonal antibody, cetuximab [18]. These agents appear efficacious and tolerable making them a good therapeutic option particularly in the elderly.

Panitumumab is a high affinity human IgG2 monoclonal antibody directed against human EGFR [19]. To date there are no studies evaluating panitumumab in advanced CSCC. We therefore aimed to investigate the efficacy of single-agent panitumumab in patients with incurable CSCC, not suitable for local therapy or chemotherapy.

### patients and methods

#### study design and objectives

The trial was an open label, uncontrolled, single centre prospective phase II study conducted at the Princess Alexandra Hospital, Brisbane, Australia.

The primary objective was to investigate the efficacy of panitumumab as a single agent as determined by the best overall response observed, according to Response Evaluation Criteria in Solid Tumours (RECIST version 1.1) criteria, following evaluation of all response assessments per time point.

Secondary end points included treatment-related acute and late toxicity according to the Common Terminology Criteria for Adverse Events (CTCAE) Version 3.0; safety based on 80% of patients commencing therapy successfully completing treatment with no treatment-related life-threatening toxicity or dose-limiting toxicity other than skin toxicity; progression-free survival (PFS) reported from the time of first study treatment to the date of disease progression of the primary, nodal or primary and nodal disease following the best treatment response or the development of distant metastases or death.

### patient eligibility

Eligible patients had histopathological or cytopathological confirmation of locally advanced, metastatic or recurrent CSCC not suitable for curative therapy with a life expectancy of >3 months and adequate haematological, hepatic and renal function.

Other eligibility included ≥18 years of age, Eastern Collaborative Oncology Group (ECOG) performance status 0–2, and the presence of at least one target lesion measurable by RECIST criteria. Patients could previously have received radiotherapy or cytotoxic chemotherapy.

Exclusions included patients receiving concurrent chemotherapy or radiotherapy, known hypersensitivity to EGFR inhibitors, clinically significant cardiovascular disease (including myocardial infarction, unstable angina, symptomatic congestive heart failure and serious uncontrolled cardiac arrhythmia) ≤1 year before enrolment/randomization and a history of interstitial lung disease, pneumonitis or pulmonary fibrosis or evidence of interstitial lung disease on previous imaging.

### study treatment

Eligible patients commenced treatment within two weeks of signing informed consent. No premedication or test dose of panitumumab was required. Panitumumab was administered at a dose of 6 mg/kg, delivered via i.v. infusion over 60 min. Panitumumab was delivered on a second weekly basis until documented progressive disease using RECIST criteria, dose-limiting toxicity or a maximum of nine cycles reached. Panitumumab dose modifications and treatment interruptions were allowed for dermatological toxicity Grade 3 CTCAE V3.0 and higher.

### assessment

All patient baseline assessments were undertaken within 2 weeks of commencing study treatment. Baseline assessment included staging, general physical examination, skin assessment, complete blood count, serum biochemistry and initial tumour biopsy for patients participating in the optional translational study (results to be published separately).

Staging included clinical examination and computer tomography (CT) scans of the head and neck, chest and abdomen. Both magnetic resonance imaging (MRI) scanning and/or positron emission tomography (PET) staging were used at baseline at investigators discretion. On follow-up for response assessment both clinical examination (for dermal disease only) and CT scanning were used but the use of MRI or PET was discretionary.
Response assessment (according to RECIST version 1.1) was undertaken after every three cycles of panitumumab by an independent radiologist. An investigator blinded to the clinical outcomes retrospectively reviewed the assessments and if there was discordance the case was adjudicated on by another radiologist blinded to previous assessments. At the time of first documented progression or completion of nine cycles of panitumumab patients had 3 monthly response assessments in the first year followed by four monthly for a minimum of 18 months from commencement of treatment or until progression or death.

**statistical analysis**

All registered patients were accounted for in the analysis and patients who commenced any therapy were assessed for the main end points of efficacy and safety. Target accrual of 16 patients was based on 4 patients (25%) exhibiting either partial (PR) or complete response (CR), allowing a response rate confidence interval (CI) estimate of 7%–52% (based on 95% two-tailed binomial limits). Since the response rate for untreated patients is 0%, a follow-up time was calculated using the reverse Kaplan–Meier method. Survival was measured through the Kaplan–Meier estimator calculated from the date of registration to all-cause death for overall survival (OS) and earliest progression for PFS.

**results**

A total of 16 patients were accrued between May 2010 and May 2012. All patients were included in the subsequent analyses.

**patient characteristics**

Of the 16 patients recruited, 14 were male and the median age 68 years. Fifteen (15/16) patients had locoregionally advanced or recurrent disease. Two of these patients also had documented distant metastatic disease. One patient had distant metastatic disease only.

Fourteen patients had received previous radiotherapy and six patients previous cytotoxic chemotherapy. Three patients received cisplatin concurrently with radiotherapy in the adjuvant setting after resection of high-risk locoregional disease. Two patients received carboplatin/5-FU for relapsed locoregional and distant disease. One patient received topical mitomycin C adjutantly for presumed superficial disease. Patient baseline characteristics are outlined in Table 1.

**response rates**

The best overall response rate (ORR; PR or CR) was 31% (95% CI 21–59%; 3/16 PR, 2/16 CR) with a further 6 of 16 patients achieving stable disease. The duration of overall response was a median 6 months (range 5–17.5 months). The 6-week disease control rate (DCR) was 69% (11 of 16 patients).

Of the patients who achieved a CR, one was in a site of distant nodal disease and the other was in both recurrent locoregional (in-transit dermal) disease and adjacent nodal disease. This was confirmed by histological examination in the latter patient. One of these patients relapsed with further distant metastatic disease at 16 months since the last dose of panitumumab. The other patient with a CR, received seven infusions of panitumumab and had no evidence of disease at 24 months since the last dose.

**measures of survival**

With a median follow-up of 24 months, 10 patients died due to progressive disease, 6 were alive, 1 patient with no evidence of disease at the time of analysis. The median OS was 11 months and median PFS was 8 months (Figure 1).

For those patients who experienced a grade 3 or 4 panitumumab-related skin toxicity, there was no relationship between this, duration of response, PFS or OS.

**panitumumab compliance and toxicity**

Of the 16 patients who commenced treatment, 9 completed all 9 planned infusions of panitumumab. Six patients ceased due to progression of disease. One patient refused further treatment after seven infusions due to grade 3 skin toxicity. This patient achieved a CR and remained disease free at the time of analysis.

Grade 3 or 4 events were observed in 5 patients. Four of these were treatment-related skin toxicity which resulted in delayed infusions or dose reductions for these patients. Treatment-related toxicities are outlined in Table 2.

**safety and tolerability**

Adverse events (AEs) were reported for all 16 patients. Significant AEs are listed in Table 2. The study was completed meeting the predetermined safety criteria of 80% of patients who commence therapy successfully completing treatment with no treatment-related life-threatening toxicity or dose-limiting toxicity other than skin toxicity. There were no panitumumab-related hypersensitivity reactions to the first infusion. Grade 3 or 4 AEs

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**Table 1. Patient baseline characteristics**

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<thead>
<tr>
<th>Baseline characteristics</th>
<th>No. of patients</th>
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occurred in 31% of patients (5 of 16 patients); 4 being skin toxicity and 1 treatment-related fatigue.

**Discussion**

Although advanced CSCC is quite common there are few prospective trials regarding its optimal management. This study demonstrates the efficacy, safety and tolerability of panitumumab in patients with incurable CSCC, not suitable for local therapy or chemotherapy.

In the phase II study reported by Maubec et al. [18], the primary end point reported was a disease control rate at 6 weeks. For these patients with unresectable CSCC, cetuximab was given as first-line treatment and the DCR at 6 weeks was 69%. The response rate was 11% at 6 weeks with a best ORR in the intention to treat population of 28%. The median duration of control was 5 months. This study reports that some patients were slow to respond to therapy. Given that some patients have an indolent course with advanced CSCC, this is not unexpected and brings into question the value of a 6-week DCR.

In the phase II study by Lewis et al. [17], gefitinib was given neoadjuvantly before surgery and/or radiotherapy with a CR in 18.2% of patients and PR in 27.3%. In our study of panitumumab, most of the patients had been pre-treated; 12 patients had previous surgery, 14 of 16 patients receiving previous radiotherapy and 7 of 16 patients having prior chemotherapy. The best ORR was 31%, with a DCR at 6 weeks of 69% and duration of response being 6 months. These figures compare favourably with the published literature using cetuximab [18] and gefitinib [17]. In this series, there also were several sustained CRs, with one patient still disease free over 2 years since registration (Figures 2 and 3).

The use of cisplatin, 5-FU and bleomycin [5] and cisplatin and doxorubicin [6] have been evaluated in up front inoperable setting. The ORRs were 84% and 68%, respectively. Responses in advanced CSCC have also been observed with a combination of IFN-α2a, 13-cRA and cisplatin biochemotherapy regimen [8]. In this setting, the overall and CR rates were reported to be 34% and 17%, respectively, which is comparable with the current study. Despite these good responses, these regimens are rarely used in clinical practice due to relatively high rates of...
The safety of single-agent panitumumab in this cohort of patients was confirmed with a 31% rate of grade 3 or 4 toxicity which was largely due to the expected skin toxicity associated with EGFR inhibitors. Although the rate of grade 3 and 4 skin toxicity is higher than the study by Maubec et al. [18], it is not uncommon in elderly patients in Australia where chronic sun-exposed skin may be a contributor [20]. We were unable to establish a relationship between panitumumab skin toxicity and duration of response, OS or PFS; however, this may reflect the small number of patients in the study.

In this study, patients were not screened before entry for overexpression of EGFR. In a translational sub-study, total EGFR expression levels were not associated with treatment efficacy. EGFR plasma membrane expression versus internalised EGFR was measured in the development of a novel assay and data will be analysed for possible correlation with treatment efficacy as a method for prediction would be clinically useful.

Finally, it must be emphasised that the efficacy of panitumumab in this study is for incurable CSCC. In mucosal squamous cell carcinoma, the combination of EGFR inhibition with chemotherapy [21] and radiotherapy [22] is well established and caution should be used in extrapolating these studies to the cutaneous setting.

**conclusions**

In conclusion, this is the first prospective trial evaluating single-agent panitumumab in the treatment of patients with incurable CSCC not suitable for local therapy. It highlights the clinical usefulness of EGFR inhibition in CSCC but also the need for molecular markers to select treatment for those most likely to respond.

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**disclosure**

The authors have declared no conflicts of interest.

**references**

Prevalence and correlates of unmet supportive care needs in patients with resected invasive cutaneous melanoma

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Background: Knowledge about supportive care needs in patients with cutaneous invasive melanoma is scarce. We examined the unmet needs of melanoma patients treated with surgery and factors associated with these needs to assist health professionals identify areas needing clinical attention.

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