EUROPEAN JOURNAL OF CANCER 45 (2009) 1589–1596

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# A randomised Phase III trial of glufosfamide compared with best supportive care in metastatic pancreatic adenocarcinoma previously treated with gemcitabine ☆

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ARTICLE INFO

*Article history:*
Received 23 October 2008
Received in revised form
16 December 2008
Accepted 17 December 2008
Available online 31 January 2009

*Keywords:*
Pancreatic neoplasms metastatic
Phase III
Glufosfamide

ABSTRACT

*Purpose:* There are currently no approved therapies for patients with metastatic pancreatic adenocarcinoma previously treated with gemcitabine. This Phase III trial evaluated the efficacy and safety of glufosfamide as compared with best supportive care (BSC) in this patient population.

*Methods:* Patients were randomised to glufosfamide plus BSC or to BSC alone with baseline performance status as a stratification factor. The primary end-point was overall survival.

*Results:* Three hundred and three patients were randomised: 148 to glufosfamide plus BSC and 155 to BSC alone. There was an 18% increase in overall survival for glufosfamide that was not statistically significant: hazard ratio (HR) 0.85 (95% confidence interval (CI) 0.66–1.08, $p = 0.19$). Median survival was 105 (range 5–875) days for glufosfamide and 84 (range 2+ to 761) days for BSC. Grade 3/4 creatinine increase occurred in 6 patients on glufosfamide, including 4 with dosing errors.

*Conclusion:* These results suggest low activity of glufosfamide in this very refractory patient population.

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## 1. Introduction

Pancreatic adenocarcinoma is notoriously difficult to be treated successfully, and patients with metastatic disease previously treated with gemcitabine have no clear options for treatment. It is estimated that there will be 37,680 new cases and 34,290 deaths from pancreatic cancer in the United States (US) in 2008.[1] The worldwide estimates for 2002 were 232,306 new cases and 227,023 deaths.[2] Gemcitabine has been the mainstay of first-line therapy for advanced disease despite very modest results,[3] and the evaluation of gemcitabine combinations has not provided substantial improvements in survival.[4,5] Second-line therapy is even more challenging. Several small Phase II studies of a variety of chemotherapeutic agents have been published with response rates from 0% to 24% and overall survival ranging from 3 to 6 months.[6–9] To date, no

☆ Presented in part at 2007 European Cancer Conference in Barcelona, Spain. Study drug was provided and study costs were paid by Threshold Pharmaceuticals.

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0959-8049/$ - see front matter © 2009 Published by Elsevier Ltd.
doi:10.1016/j.ejca.2008.12.022

Phase III trials in patients with pancreatic cancer previously treated with gemcitabine have been published in full. One abstract reports a significant increase in overall survival (median of 26 versus 13 weeks; $p = 0.014$) with the addition of oxaliplatin to 5-fluorouracil/folinic acid.[10]

Glufosfamide consists of the active metabolite of ifosfamide, isophosphoramide mustard (IPM), linked to β-D-glucose. Malignant cells utilise glucose at a higher rate than normal cells and express higher levels of glucose transporters, which may lead to preferential uptake of glufosfamide by malignant cells. Unlike ifosfamide, glufosfamide is not metabolised to acrolein, the cause of haemorrhagic cystitis.[11] In addition, based on the animal studies, the amount of metabolically generated toxic chloroacetaldehyde after glufosfamide is only a small fraction of that generated after ifosfamide (unpublished data). Chloroacetaldehyde production is believed to play a role in ifosfamide-induced neurotoxicity and nephrotoxicity.

A Phase II study of glufosfamide (5000 mg/m$^2$ intravenously over 1 h every 3 weeks) was performed in 34 patients with chemotherapy-naïve advanced pancreatic cancer. Two of the 34 subjects achieved a partial response and 11 other subjects had stable disease based on an independent review.[12] Median survival and progression-free survival were 5.4 and 1.6 months. In a Phase I study of 6-h infusion of glufosfamide for patients with solid tumours, the one patient enrolled with locally advanced pancreatic cancer was treated with 4500 mg/m$^2$ and had a long-term (>6 years) complete response.[13] Ifosfamide has shown some evidence of activity in pancreatic cancer.[14] Based on these data, a Phase III trial of glufosfamide was performed in patients with metastatic pancreatic cancer that had relapsed after treatment with gemcitabine. As no therapy has demonstrated clinical benefit for patients relapsing after gemcitabine, a control arm of best supportive care (BSC) was selected as the randomised comparator.

## 2. Patients and methods

### 2.1. Patients

Eligible patients had metastatic pancreatic adenocarcinoma that had progressed during or after treatment with gemcitabine for advanced disease. Only patients with distant metastases were eligible. Patients were at least 18 years of age, had at least one target or non-target lesion by RECIST,[15] had recovered from reversible toxicities of prior therapy, had adequate organ reserve including haematopoietic, hepatic and renal function (CrCL $\geqslant$ 1.0 mL/s calculated by the Cockcroft-Gault formula) and had a Karnofsky performance status (KPS) of at least 70. Patients were excluded if they had received more than one prior systemic therapy regimen for advanced disease. This study was reviewed and approved by local institutional review boards/ethics committees, and all participating patients signed an approved informed consent form. The trial was conducted according to Good Clinical Practice guidelines.

### 2.2. Study design and treatment

In this open-label, international study, patients were randomly (1:1) assigned to receive glufosfamide plus BSC or BSC alone. Randomisation was stratified by KPS (70 versus $\geqslant$80). Glufosfamide (4500 mg/m$^2$) was administered intravenously over 6 h (1/4 over 30 min; 3/4 over 5.5 h) on day 1 of every 3-week cycle. BSC was defined as analgesics, antibiotics, transfusions, therapeutic haematopoietic colony-stimulating factors, erythropoietin and other appropriate supportive measures including concomitant medications that do not have anti-tumour effects. Megestrol acetate for appetite stimulation was permitted. Glufosfamide was withheld if grade 2 or greater drug-related toxicity (other than alopecia, nausea, vomiting) occurred and was resumed with a 25% dose reduction for grade 3 or 4 toxicity. Glufosfamide was withheld for an increase in bilirubin >1.5 × upper limit of normal or CrCL < 1.0 mL/s, regardless of whether it was study drug-related. A confirmed drop in CrCL to <1.0 mL/s required that glufosfamide be discontinued. Adverse events were assessed using the National Cancer Institute's Common Toxicity Criteria (CTCAE v3.0).[16] Patients in both treatment arms were seen every 3 weeks. Tumour assessments were performed every 2 cycles (6 weeks) for the first 8 cycles and every 3 cycles thereafter. Response assessments were performed by investigators based on RECIST.[15] Serum CA 19-9 was measured every cycle for the first 8 cycles and every 3 cycles thereafter. Pain assessments evaluating pain intensity in the previous 24 h using a 100-mm visual analogue scale (VAS) were performed on day 1 of every cycle and at study termination. Patients were followed every 3 months for survival.

The primary efficacy end-point was overall survival, defined as the time from randomisation to death from any cause. Secondary efficacy end-points were progression-free survival, defined as the time from randomisation to documented disease progression or death on study (excluding the survival follow-up period), confirmed response rate, duration of response, best response of stable disease or better, 6-month survival and 12-month survival, serum CA 19-9 response, VAS pain intensity and KPS. A serum CA 19-9 response was defined as a decrease of at least 50% from the baseline CA 19-9.

### 2.3. Statistical analysis

Primary analysis was conducted after the 258th death was reported. Based on a two-sided log-rank test with an alpha of 5%, this design had 90% power to detect a 50% improvement in median survival. A median survival of 4.5 months in the glufosfamide-treated group, a median survival of 3 months in the BSC group, a dropout rate of 10% and 12-month accrual with 24-month follow-up were anticipated. All efficacy analyses were performed using the intent-to-treat population unless otherwise specified. The date of the 258th death determined the data cutoff date for the primary analysis. A final survival sweep was conducted to determine 12-month survival and update efficacy duration measures. All reported efficacy and safety analyses were based on the final survival sweep data with the exception of the primary efficacy analysis of overall survival and progression-free survival. The safety analysis population included all patients who received glufosfamide and all patients in the BSC arm who had a Cycle 1/Day 1 visit. The adverse event reporting period was from the first dose of glufosfamide until 30 days after the last dose for

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