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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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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.

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

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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

the glufosfamide arm and from the Cycle 1/Day 1 visit until study discontinuation for the BSC arm.

An independent data monitoring committee (IDMC) reviewed safety data on a monthly basis until the interim analysis. One interim analysis for efficacy and safety was performed after 126 deaths had occurred. Lan and DeMets[17] implementation of the O'Brien and Fleming[18] group sequential method was used to determine the stopping boundaries. The IDMC recommended continuing the study. For the final analysis, a p-value < 0.04911 was considered statistically significant.

A two-sided stratified log-rank test with one stratification factor: baseline KPS (80–100 versus <80) was used to compare overall survival and progression-free survival. The Kaplan-Meier product limit method was used for survival estimates. The 6-month survival and 12-month survival were compared using a Z test with standard errors calculated using Greenwood's formula. Fisher's exact test was used to compare response rates and stable disease or better rates. For continuous efficacy measures, a paired t-test was used for the test of mean change from baseline to follow-up visit within each treatment group. A two-sample t-test was used to make comparisons between treatment groups.

3. Results

Three hundred and three patients were randomised at 90 centres in 11 countries between September 2004 and August 2006, 148 to glufosfamide and 155 to BSC. The database for the primary efficacy analysis of survival and progression-free survival included all data through 7th January 2007, at which time 261 deaths had occurred. Other efficacy end-points and all safety analyses were updated through 10th August 2007 at which time all patients had completed the active part of the study and 282 patients had died.

3.1. Patient population

Patient characteristics were similar between treatment groups except for a trend of more patients in the glufosfamide arm with low serum albumin at baseline ($p = 0.11$) or being 65 years of age or older ($p = 0.06$) (Table 1). All patients had received gemcitabine, 29 (10%) had received radiotherapy and 68 (22%) had prior pancreatic resection. Baseline target lesions were reported for 287 (95%) of patients, and non-target lesions were reported for 250 (83%) of patients. Fourteen subjects did not meet all study eligibility criteria, 4 in the glufosfamide arm and 10 in the BSC arm. Significant violations were: two patients had ineligible histology (adenocarcinoma of the Ampulla of Vater, pseudopapillary carcinoma of the pancreas), one had no detectable lesions with an elevated CA 19-9, five had only locally advanced disease and three received only adjuvant gemcitabine.

Seven patients on the glufosfamide arm did not receive glufosfamide and 10 patients on the BSC arm discontinued between randomisation and the first study visit (Fig. 1). There was an imbalance in dropout rates between the treatment groups, primarily because 20 patients in the BSC arm discontinued because they did not want to be in the BSC arm. The majority of patients discontinued from the study for progressive disease, and discontinuation for adverse events was not more common in the glufosfamide arm (Fig. 1).

Table 1 – Baseline characteristics of all randomised patients.

Characteristic	Glufosfamide	BSC
	N = 148	N = 155
Age, years		
Median	58	57
Range	27–78	29–80
Age ⩾ 65 years – no. (%)	40 (27)	28 (18)
Gender – no. (%)		
Male	90 (61)	90 (58)
Female	58 (39)	65 (42)
Race – no. (%)		
White	129 (87)	134 (87)
Other	19 (13)	21 (14)
Region – no. (%)		
Europe	62 (42)	63 (41)
Russia	41 (28)	39 (25)
Mexico/South America	26 (18)	35 (23)
United States	10 (7)	11 (7)
India	9 (6)	7 (5)
Karnofsky Performance Status – no. (%)		
100	23 (16)	20 (13)
90	36 (24)	48 (31)
80	62 (42)	62 (40)
70	27 (18)	25 (16)
Sites of metastatic disease – no. (%)		
Liver	114 (77)	120 (80)
Non-liver	34 (23)	35 (20)
Months from initial diagnosis		
Median	6.1	6.1
Range	1.3–51	1.2–38
Best Response to Gemcitabine – no. (%)		
Complete response	4 (3)	4 (3)
Partial response	12 (8)	12 (8)
Stable disease	41 (28)	50 (32)
Progressive disease	84 (57)	83 (54)
Unknown	7 (5)	6 (4)
Serum Albumin – no. (%)		
<33 g/L	50 (34)	39 (26)
⩾33 g/L	96 (66)	112 (74)
Back or abdominal pain – no. (%)		
Yes	122 (82)	129 (83)
No	26 (18)	26 (17)
>10% Weight loss in past 6 months – no. (%)		
Yes	53 (36)	63 (41)
No	83 (56)	86 (56)
Unknown	12 (8)	6 (4)
CA 19-9 – no. (%)		
>Twice upper limit of normal	96 (76)	87 (76)
	N = 126	N = 115

3.2. Efficacy analyses

There was an 18% improvement in overall survival for glufosfamide that was not statistically significant. The hazard

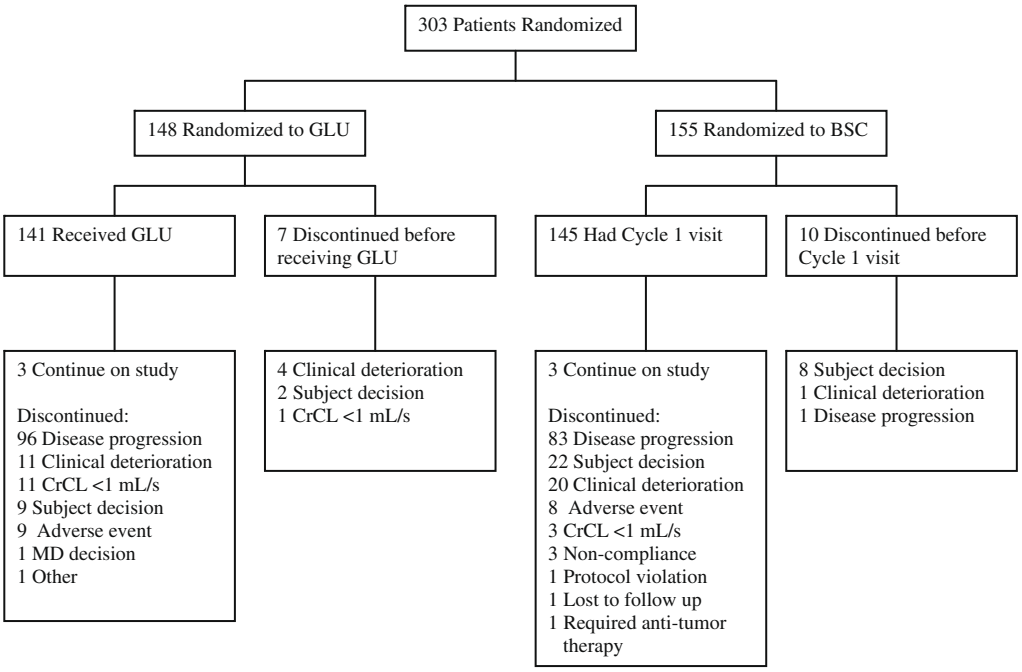

Fig. 1 – Patient randomisation and disposition at the time of final analysis after 261 deaths.

ratio (HR) was 0.85 (95% confidence interval (CI) 0.66–1.08) with a *p*-value of 0.187. The median survival was 105 (range 5–875) days in the glufosfamide arm and 84 (range 2+ to 761) days in the BSC arm, a difference of 3 weeks. Kaplan-Meier curve is shown in Fig. 2. The hazard ratio was also not significant in the subgroup of patients with baseline KPS of at least 80. Six-month survival and 12-month survival were 28% and 18% in the glufosfamide arm, not statistically significant compared with 28% and 16% in the BSC arm. Median survival and progression-free survival were 46 (range 1+ to 351) and 43 (range 1+ to 372) days with a hazard ratio of 0.76 (95% CI 0.57–1.02) and *p*-value of 0.06. A large number, 110 patients, were censored for this end-point, primarily because of study discontinuation for clinically significant deterioration that did not meet the criteria for disease progression.

There were no complete responses. Three patients in the glufosfamide arm and one in the BSC arm had confirmed partial responses. A significant number of patients had no post-baseline tumour assessment (30% in glufosfamide arm and 46% in BSC arm), and were assumed to have progressive disease for response analysis. Duration of response ranged from 47+ to 277+ days. Stable disease or better was the best response in 31% on the glufosfamide arm and 19% on the BSC arm. This difference was statistically significant ($p = 0.016$).

Serum CA 19-9 was elevated at baseline in 76% of patients who had a sample drawn. For patients with an elevated CA

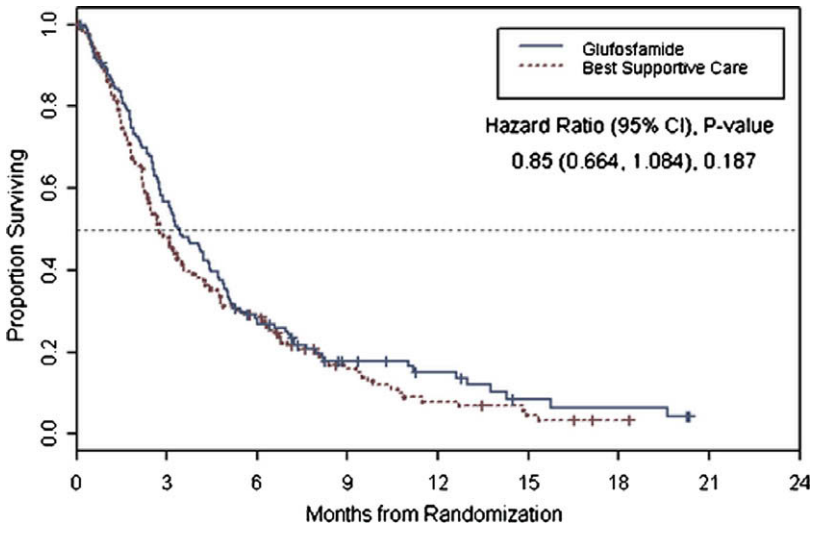

Fig. 2 – Overall survival for all randomised patients (intent-to-treat population; at the time of final analysis after 261 deaths).

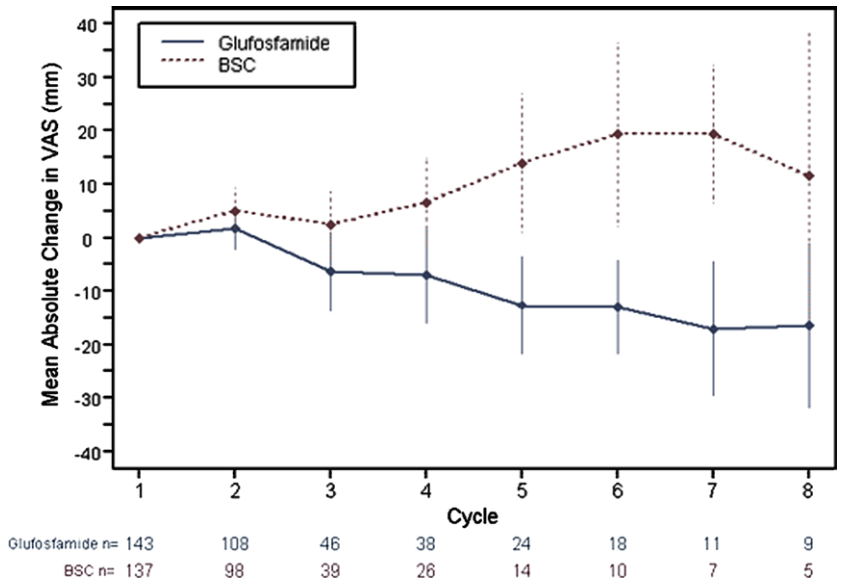

Fig. 3 – Mean change (mm) in 100 mm visual analogue pain score with 95% confidence intervals (CI).

19-9 at baseline (>twice the upper limit of normal) and at least one follow-up measurement, CA 19-9 response was documented in 11 (16.2%) of 68 subjects on the glufosfamide arm and in 5 (8.9%) of 56 in the BSC arm ($p = 0.28$).

VAS pain score decreased in the glufosfamide arm and increased on BSC (Fig. 3). This was not due to better pain management in the glufosfamide arm as a higher proportion of subjects in the glufosfamide arm had no increase in VAS pain score for at least 2 consecutive cycles without a concomitant increase in narcotic analgesic use (72% versus 44%, $p = 0.02$; analysis included only subjects on study for at least 3 cycles).

Thirty four of 148 (23%) patients in the glufosfamide arm and 38 of 155 (25%) in the BSC arm had systemic anti-tumour therapy after study discontinuation including 14 of the 20 patients in the BSC arm who discontinued from the study because they were randomised to BSC.

3.3. *Exploratory analyses*

Baseline factors that were found to be predictive of poor survival, regardless of the treatment group included baseline albumin <33 g/L, Karnofsky performance status < 80, >10% weight loss in past 6 months, presence of liver metastases, back or abdominal pain and baseline VAS pain score ⩾ 20 mm. Survival was compared across countries within and between groups. Overall there were no significant differences in survival between countries. The difference in survival between glufosfamide and BSC was greatest in the United States (hazard ratio = 0.34, $p = 0.041$) and smallest in India (hazard ratio = 2.52, $p = 0.150$).

Given the structure of glufosfamide, glucose conjugated to IPM, glufosfamide activity was analysed in diabetic patients and in subgroups of diabetics based on their concomitant medications. The effect of glufosfamide appeared limited to patients without a history of diabetes (hazard ratio = 0.78). However, within the diabetic subgroup, 18 patients who were on insulin did poorly on glufosfamide (median survival = 85 days; range 12 to 590+ days), and the 7 patients who were on an oral glucose-lowering agent and not on insulin had the most evidence of a glufosfamide effect (median survival = 418 days; range 54–643 days) with a hazard ratio of 0.18. In addition, regardless of diabetic status, patients with an elevated baseline glucose including some of the patients on glucose-lowering medications had evidence of a glufosfamide effect with a hazard ratio of 0.37.

3.4. *Adverse events*

The median time on study was 2 (range 0–14) cycles for both treatment arms with only 29% of the patients on the glufosfamide arm and 26% of the patients on the BSC arm continuing on study to Cycle 3.

Table 2 – Severe (grades 3, 4 and 5) adverse events occurring in at least 2% of glufosfamide patients.

Preferred term (MedDRA)	Glufosfamide N = 141	BSC N = 145
Any adverse event	63 (44.7%)	44 (30.3%)
Asthenia/fatigue[a]	12 (8.5%)	11 (7.6%)
Abdominal pain[b]	11 (7.8%)	13 (9.0%)
Anaemia	7 (5.0%)	3 (2.1%)
Vomiting	7 (5.0%)	2 (1.4%)
Nausea	6 (4.3%)	2 (1.4%)
Deep vein thrombosis	5 (3.5%)	1 (0.7%)
Renal failure	5 (3.5%)	0 (0%)
Hyperbilirubinaemia	4 (2.8%)	2 (1.4%)
Leucopenia	4 (2.8%)	0 (0%)
Anorexia	3 (2.1%)	2 (1.4%)
Hyperglycaemia	3 (2.1%)	1 (0.7%)
Hypokalaemia	3 (2.1%)	0 (0%)

a Asthenia and fatigue preferred terms combined because combined in CTCAE v3.
b Includes abdominal pain and abdominal pain upper.

The majority of the patients (92%) died from progressive pancreatic cancer. Five patients in the glufosfamide arm and six in the BSC arm died from adverse events. The five events in the glufosfamide arm were renal failure (2), aspiration, vomiting and sepsis. Death within 30 days of randomisation occurred in 13% of patients in the glufosfamide arm and 15% in the BSC arm. Serious adverse events occurred in 16% of subjects on glufosfamide and 10% on BSC.

The most common non-laboratory adverse events were nausea, asthenia/fatigue, abdominal pain and vomiting. Severe (grade 3 or greater) adverse events that were more common in the glufosfamide arm were vomiting, nausea, deep venous thrombosis and renal failure (Table 2). Grade 3 or 4 haematologic toxicity was uncommon but was more frequent in the glufosfamide arm. Febrile neutropaenia was not reported.

For subjects with CrCL $\geqslant$ 1.0 mL/s at Cycle 1/Day 1 and at least one follow-up measurement, CrCL fell to <1 in 36 of 127 (28%) subjects in the glufosfamide arm and 15 of 111 (14%) subjects in the BSC arm. Hypokalaemia and hypophosphataemia were more common in the glufosfamide arm. Severe nephrotoxicity (grades 3–5) occurred only in the glufosfamide arm. Four patients developed a grade 4 increase in serum creatinine, and two patients had a grade 3 increase. Four of these six patients had significant glufosfamide dosing errors (treated when CrCL < 1 mL/s, bilirubin > 1.5 × upper limit of normal or grade 3 hypophosphataemia) that may have contributed to the development of nephrotoxicity.

4. Discussion

This international, randomised, Phase III trial failed to meet its primary end-point of a statistically significant improvement in overall survival as compared with best supportive care in patients who had progressed after receiving a first-line gemcitabine-containing regimen. However, the non-significant improvement in overall survival and differences in several secondary end-points suggest that there was anti-tumour activity of glufosfamide in this refractory patient population. Clinical benefit rate (partial response plus stable disease for at least 6 weeks), progression-free survival and CA19-9 response were all superior in patients in the glufosfamide arm, although the differences could not be considered clinically meaningful. Additionally, VAS pain score significantly improved on glufosfamide but worsened on BSC, and the improvement was not due to increased use of narcotic analgesics in the glufosfamide arm.

While this trial shows that glufosfamide has some activity in patients with metastatic pancreatic cancer previously treated with gemcitabine, the majority of patients deteriorated too quickly for an adequate trial of therapy. Rapid clinically significant deterioration resulted in 35 (12%) patients (13 in the glufosfamide arm and 22 in the BSC arm) having no post-baseline tumour assessment. Other major reasons for no post-baseline tumour assessment were patient decision (14%, primarily because not randomised to glufosfamide arm) and adverse event (7%). This high early dropout rate makes the progression-free survival end-point less reliable. As only 5 patients were not available for survival follow-up, four who withdrew consent for survival follow-up and one who was lost to follow-up, the overall survival result is robust.

This is the first reported randomised Phase III study in second-line metastatic pancreatic cancer. The patient population studied had a very poor prognosis. Unlike most other oncology studies, there was no eligibility criterion restricting enrollment to subjects with expected survival of at least 3 months. Patients with locally advanced disease alone were excluded, and very few (11%) had responded to previous gemcitabine treatment. Because over 70% of patients were on study for 2 or fewer cycles, exposure to glufosfamide was limited. Future controlled studies in this patient population may require restricting enrollment to subjects with better performance status. While 42% of subjects with a KPS of 70 received either one cycle or no cycles, 31% of subjects with KPS of greater than 70 received either one cycle or no cycles. A second study design issue involved subject discontinuation after randomisation to best supportive care. Sites were trained to make every effort not to randomise patients who were likely to discontinue from the study if randomised to BSC but this did not prevent the problem. A placebo control was considered but rejected because of the requirement for intravenous administration.

As compared with BSC alone, glufosfamide was associated with an increase in adverse events including renal failure, nausea, vomiting, diarrhoea, constipation and deep vein thrombosis. However, the majority of these events were not severe, and did not result in discontinuation of therapy. Renal failure occurred in less than 5% of patients, and the primary risk factors were dosing errors and reduced renal function at baseline. It is possible that there may be a component of renal hypoperfusion in the cases of nephrotoxicity. Of the 6 subjects with grade 3/4/5 nephrotoxicity, 2 were hypotensive at the time of the last dose before renal insufficiency, 1 was on substantial doses of NSAIDs, 3 had chronic hypertension, 1 was on an ACE inhibitor, 3 were on diuretics, 3 had atherosclerosis and 3 had diabetes, all potential risk factors for renal hypoperfusion.[19] Elevated serum bilirubin, which could lead to reduced biliary clearance of glufosfamide, may also increase the risk of renal dysfunction. The lack of neurotoxicity and the presence of nephrotoxicity suggest that these known toxicities of oxazaphosphorine drugs are not caused by the same molecule or that there is a differential metabolism of ifosfamide and glufosfamide in kidney and brain.

Subgroup analyses indicated that glufosfamide may have enhanced activity relative to BSC in diabetic patients receiving oral hypoglycaemic agents or patients with elevated serum glucose, but reduced activity in diabetics receiving insulin; however, given the exploratory nature of the findings and the limited number of patients in the respective subgroups, it would require confirmation in another study. Given that glufosfamide is a glucose-conjugated prodrug,[20] it is possible that the subgroup response differences are due to the differences in prodrug cellular uptake or prodrug activation (glycosidic bond cleavage). Antidiabetic sulfonylureas have been shown to upregulate the expression and activity of glucose transporters.[21,22] Conversely, glucose transporter expression has been shown to be downregulated by hyperinsulinaemia and upregulated by hyperglycaemia.[23] Insulin levels have also been shown to modulate the activities of the

glucuronidase enzyme heparanase,[24] and glucuronidase activity has been shown to activate glufosfamide.[25] However, the mechanistic basis for the apparent subgroup response differences remains to be elucidated.

This study also provides valuable information on the natural history of metastatic pancreatic cancer previously treated with gemcitabine. The very poor prognosis with rapid clinical deterioration suggests that it will be very difficult to find effective therapies for these patients. Given the positive result reported in the CONKO-003 study with oxaliplatin and 5-fluorouracil, future trials for second-line therapy should consider combination therapy.[10]

Conflict of interest statement

Stewart Kroll is an employee of and has stock holdings in Threshold Pharmaceuticals. Virginia Langmuir and George Tidmarsh are consultants for and have stock holdings in Threshold Pharmaceuticals.

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