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# Glufosfamide administered using a 1-hour infusion given as first-line treatment for advanced pancreatic cancer. A phase II trial of the EORTC-new drug development group☆

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**Abstract**

The activity of glufosfamide (β-D-glucopyranosyl-*N*,*N*′-di-(2-chloroethyl)-phosphoric acid diamide) against pancreatic cancer was investigated in a multicentre, phase II clinical study. Chemotherapy-naïve patients with advanced or metastatic disease were treated with glufosfamide (5 g/m$^2$) using a 1-h intravenous (i.v.) infusion every 3 weeks. Patients were randomised between active-hydration and normal fluids to evaluate the nephroprotective effect of forced diuresis. Patients experiencing >0.4 mg/dl (>35 μmol/l) increase in serum creatinine compared with their baseline value were taken off treatment for safety reasons. The evaluation of response was according to the Response evaluation criteria in solid tumours (RECIST). Blood sampling was performed for pharmacokinetic analyses. 35 patients from 13 institutions were registered over a 13-month period. A total of 114 treatment cycles (median 3, range 1–8) were administered to 34 patients; 18 patients were allocated to the hydration arm. Overall haematological toxicity was mild. Metabolic acidosis occurred in 2 patients treated in the active-hydration arm, grade 3 hypokalaemia was recorded in 5 patients and grade 3 hypophosphataemia in 4 patients. One patient had a grade 4 increase in serum creatinine level, concomitantly to disease progression. Active-hydration did not show a nephroprotective effect and the plasma pharmacokinetics (Pk) of glufosfamide was not significantly influenced by hydration. Two confirmed partial remissions (PR) were reported (response rate 5.9%, 95% Confidence Interval (CI) 0.7–19.7%) and 11 cases obtained disease stabilisation (32.4%). An extra mural review panel confirmed all of the responses. Median overall survival was 5.3 months (95% CI 3.9–7.1) and time to progression (TTP) was 1.4 months (95% CI 1.3–2.7). In conclusion, glufosfamide administered using a 1-h infusion every 3 weeks has a modest activity in advanced pancreatic adenocarcinoma. Haematological toxicity is particularly mild, but regular monitoring of renal function is recommended.


*Keywords:* Glucosfamide; D-19575, Pancreatic-cancer; Chemotherapy, Phase II

## 1. Introduction

Adenocarcinoma of the pancreas represents approximately 3% of all malignancies diagnosed and accounts for 6–10% of cancer deaths in different European countries [1].

To date, surgical resection offers the only chance for long-term survival [2,3]. For most patients, there is no

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effective treatment currently available, as they present with advanced disease at diagnosis. More than 30 chemotherapeutic agents have been investigated over the last 20 years with frustrating results. Response rates of below 10% were obtained when subjected to external review validation and a median survival of less than 6 months was reported [4]. Gemcitabine has been accepted as the reference chemotherapeutic agent for advanced pancreatic cancer on the basis of its superiority with regard to clinical benefit response and survival when compared with 5-fluorouracil [5]. Combinations of gemcitabine with other agents have so far failed to further improve the duration of survival in this patient population, while initial results of novel chemotherapy combinations are yet to be confirmed in randomised studies [6–9]. The overall poor results of currently available therapies emphasise the need to develop effective drugs for this disease [10].

Glufosfamide is an alkylating agent that the European Organisation for Research and Treatment of Cancer (EORTC) have tested clinically for activity in advanced or metastatic pancreatic cancer, following completion of a phase I study that showed antitumour activity in pancreatic cancer (a complete response was achieved in one patient that lasted for more than 4 years) and other tumour types [11]. Some activity has also been reported for a related compound, ifosfamide [12,13]. The overexpression of glucose transporters has also been reported in pancreatic carcinoma [14]. Glufosfamide (Fig. 1) has an active alkylating moiety isophosphoramide mustard linked to β-D-glucose that gives it the potential to exploit the transmembrane transport system of glucose [15]. It has been shown that glufosfamide is conveyed into tumour cells by SAAT1, a low-affinity sodium-dependent β-D-glucose co-transporter, while other glucose transporters may also play a role in the intracellular translocation of this compound [16]. Together with the accelerated metabolic rate and glucose consumption of tumour cells, this targeting mechanism probably contributes to the tumour selectivity of the study drug.

We report, here, the results of the completed phase II EORTC study 16994P that evaluated the activity and toxicity of glufosfamide when given as first-line chemotherapy by a 1-h infusion every 3 weeks in patients with locally advanced or metastatic pancreatic cancer.

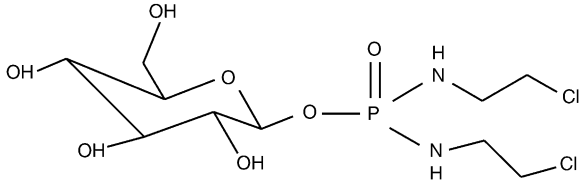


Fig. 1. Structural formula of glufosfamide.

## 2. Patients and methods

### 2.1. Study design—objectives

This was a prospective, multicentre, randomised phase II study (EORTC 16994P) conducted by the EORTC-New Drug Development Group and monitored by the EORTC Data Center. The study was performed in accordance to the Helsinki Declaration and according to the European guidelines for good clinical practice. The primary objective was to determine the antitumour activity of glufosfamide in advanced or metastatic pancreatic cancer. Secondary objectives were to determine the duration of objective response, to characterise the toxicities and to assess the impact of forced diuresis (hydration scheme) on renal toxicity. An additional objective was to assess the pharmacokinetic profile of glufosfamide in this regimen. Patients were randomly assigned to a hydration or a non-hydration arm.

Previously available data concerning dose scheduling was available from two phase I studies. In the first trial, glufosfamide was administered over a short infusion time (30–60 min) every 3 weeks (unpublished data in file). The second study evaluated a 6-h biphasic infusion schedule [11]. The shorter infusion schedule was selected for practical reasons as neither phase I study demonstrated superiority over the other with respect to the toxicity profile or antitumour activity.

### 2.2. Patient registration

Prior to treatment initiation, patients were required to register at the EORTC Data Center (Brussels, Belgium). Study eligibility included: histologically- or cytologically-proven pancreatic adenocarcinoma, metastatic or inoperable locally advanced disease, no previous chemotherapy, at least one target lesion accurately measured in the longest diameter, Eastern Co-operative Oncology group performance status (ECOG PS) $\leqslant 2$, use of effective contraception if of reproductive age, normal haematological functions assessed by an absolute neutrophil count $\geqslant 1.5\times10^9$/l, platelets $>100\times10^9$/l, normal liver functions, serum creatinine $\leqslant 150$ μmol/l and calculated creatinine clearance $\geqslant 1$ ml/s (formula of Cockcroft and Gault) [17], normal cardiac function with no history of ischaemic heart disease or congestive heart failure in the past 6 months and normal 12-lead electrocardiograph (ECG). Patients signed written informed consent before registration.

### 2.3. Treatment regimen

Patients received 5 g/m$^2$ glufosfamide diluted in 1000 ml NaCl (0.9%) that was administered intravenously (i.v.) over 60 min every 3 weeks. Patients randomised to

the active-hydration arm received 2 l of glucose 5% and NaCl 0.9% (1:1) plus 20 meq KCl per litre over a period of 4 h before, and the same after chemotherapy. Treatment was continued for a maximum of six cycles in patients with objective responses or stabilisation of disease, or until the occurrence of unacceptable toxicity, patient refusal or disease progression. For safety reasons, patients experiencing an increase above baseline in serum creatinine of $\geqslant$0.4 mg/dl (or $\geqslant$35 μmol/l) measured twice within a 1-week period were taken off the treatment.

### 2.4. Clinical evaluation

Efficacy and toxicity analyses were applied to patients who received at least one course of chemotherapy.

Response evaluation was assessed using imaging techniques on the basis of a set of 'target lesions' (any or all lesions that were measurable on study entry) selected before the first treatment administration. Assessment of response was repeated every two cycles while the patient was on treatment, and thereafter every 6 weeks until documented disease progression. The Response evaluation criteria in solid tumours (RECIST) criteria for response evaluation were applied [18]. The response rate and its 80% Confidence Interval (CI) (in order to respect the choice of the type I error in the design) were to be calculated by pooling all complete and partial responses. Overall survival (OS) and progression-free survival (PFS) were estimated using the method of Brookmeyer and Crowley [19]; they were calculated from the first day of treatment. The duration of OS was measured until the date of death or was censored at follow-up. The duration of response was measured from the date a first objective response was documented until the first sign of progression was assessed by an imaging/radiological method.

Toxicity was assessed for each cycle of therapy. The international Common Toxicity Criteria (CTC) version 2.0 were used for the evaluation of toxicity [20].

### 2.5. Pharmacokinetics

Heparinised blood (5 ml each) was collected from patients during the first course of treatment at the following time points: 0 h (pre-glufosfamide infusion), +1 h (end of infusion), +3 and +8 h. Each sample was processed and the plasma extracted, they were stored at −80 °C and shipped on dry ice to VIATRIS (Frankfurt, Germany), where the storage continued at −20 °C until analysis. An analysis of plasma samples was conducted using a validated high performance liquid chromatographic-mass spectrometry (HPLC-MS) method that employs chromatographic separation and mass spectrometric detection (Analytico Research B.V., 1998, 2000). All test samples and quality control samples were analysed following appropriate dilution. The lower limit of quantification for the determination of glufosfamide was 1 μg/ml, with a limit of detection of 0.5 μg/ml.

Plasma concentrations were evaluated by non-compartmental pharmacokinetic analysis using validated Excel based software (FUNCALC 2, 2001). For statistical analysis of pharmacokinetics, an ANOVA model with factors hydration, gender and hydration*gender was fitted to the log-transformed pharmacokinetic parameters ($C_{max}$, $t_{1/2}$, area under the curve (AUC) and clearance (CL)). The mean square errors obtained in this model were used to calculate the 90% CIs for the expected difference after re-transformation for the expected ratio in parameters between actively-hydrated and non-actively-hydrated patients, as well as between male and female patients.

### 2.6. Statistics

The two-stage Simon Design was followed for sample size determination and the decision rule regarding the response rate. According to that design, in a first step 16 patients were needed to assure, with 95% power and a type I error of 20%, that if no response was seen, the true response rate would be $\leqslant$5% and the study should be stopped. If at least one of these patients responded then 16 more patients could be registered to show that if the true response rate was 20%, the regimen could be recommended for further investigation in phase III studies.

## 3. Results

### 3.1. Demographics

Between February 2000 and March 2001, 35 patients from 13 institutions were enrolled into the study. All patients were eligible. However, 1 patient did not start treatment as a result of early death due to malignant disease progression. All analyses were therefore carried out on the 34 eligible patients who received at least one glufosfamide treatment. 18 patients were allocated to the active-hydration arm and 16 to the non-active-hydration arm.

The main clinical characteristics at study entry are listed in Table 1. The median age was 58.1 years (range 42.6–75.5) and the performance status (PS) distribution was 32, 50 and 18% for PS of 0, 1 and 2, respectively. 7 patients (21%) had a medical history of diabetes mellitus. No patient had received prior radiotherapy, while 2 patients had received prior adjuvant chemotherapy, and 50% had undergone exploratory laparotomy with a tumour biopsy. Most patients (85%) had metastatic disease at the time of registration; the remaining

patients were eligible because they had locally advanced disease or a non-resectable primary tumour.

### 3.2. Treatment

The median duration of treatment was three cycles (range 1–8), while 6/34 (18%) patients completed at least six cycles of treatment. 5 patients received the protocol treatment after the date of progression, as assessed by the extra mural review panel of tumour response to treatment. Details of drug delivery are shown in Table 2. The only reason for not receiving the planned dose intensity was due to a treatment delay, which occurred in 26% of the patients and in 11% of the cycles. This was mainly due to logistic reasons, but also related to haematological (2 patients, five cycles) and in 1 case to non-haematological toxicity. The major reason for treatment discontinuation was disease progression, reported for 28 patients (82%) (Table 3).

### 3.3. Efficacy

The response rate of glufosfamide for the assessable patients in this first-line setting was 2/34 (5.9%) (95% CI (0.7–19.7%) (Table 4). Two confirmed partial responses were observed with duration's lasting 3.2 and 6.8 months, respectively. In another 11 cases (32%), stabilisation of disease was ovserved. The overall median survival for the entire group was 5.3 months (95% CI 3.9–7.1) and time to progression (TTP) was 1.4 months (95% CI 1.3–2.7) according to the Brookmeyer and Crowley method [19]. Two early deaths occurred attributable to malignant disease progression; 1 patient was not assessable for efficacy due to a lack of imaging data.

### 3.4. Toxicity

Haematological toxicities were reported as grades 3–4 in 5 patients for uncomplicated neutropenia and or leucopenia. Grade 3 thrombocytopenia and anaemia were observed in 2 and 3 patients respectively (Table 5).

Table 1
Clinical characteristics at study entry

| Demographic data | Treatment | | |
|---|---|---|---|
| | No hydration ($N=16$) $N$ (%) | Hydration ($N=18$) $N$ (%) | Total ($N=34$) $N$ (%) |
| Age (years) | | | |
| Median (range) | 57.7 (47.7–75.5) | 58.1 (42.6–73.2) | 58.1 (42.6–75.5) |
| Gender | | | |
| Male | 9 (56) | 13 (72) | 22 (65) |
| Female | 7 (44) | 5 (28) | 12 (35) |
| Initial PS | | | |
| 0 | 4 (25) | 7 (39) | 11 (32) |
| 1 | 10 (63) | 7 (39) | 17 (50) |
| 2 | 2 (13) | 4 (22) | 6 (18) |
| Stage of disease | | | |
| I | 1 (6) | 0 | 1 (3) |
| II | 0 | 1 (6) | 1 (3) |
| III | 2 (13) | 0 | 2 (6) |
| IVa | 2 (13) | 3 (17) | 5 (15) |
| IVb | 11 (69) | 13 (72) | 24 (71) |
| Undefined | 0 | 1 (6) | 1 (3) |
| Associated chronic disease | | | |
| No | 10 (63) | 11 (61) | 21 (62) |
| Yes | 6 (38) | 7 (39) | 13 (38) |
| Prior surgery | | | |
| No | 8 (50) | 9 (50) | 17 (50) |
| Yes, curative | 2 (13) | 2 (11) | 4 (12) |
| Yes, palliative | 3 (19) | 3 (17) | 6 (18) |
| Other | 3 (19) | 4 (22) | 7 (21) |
| Prior chemotherapy | | | |
| No | 14 (88) | 18 (100) | 32 (94) |
| Yes, adjuvant only | 2 (12) | 0 | 2 (6) |

Table 2
Treatment information

| Variable | Treatment | |
|---|---|---|
| | No hydration ($N=16$) $N$ (%) | Hydration ($N=18$)[a] $N$ (%) |
| 1 cycle administered | 1 (6) | 2 (11) |
| 2 cycles administered | 6 (38) | 6 (33) |
| 3 cycles administered | 2 (13) | 2 (11) |
| 4 cycles administered | 4 (25) | 4 (22) |
| 5 cycles administered | 0 | 1 (6) |
| 6 cycles administered | 3 (19) | 2 (11) |
| 8 cycles administered | 0 | 1 (6) |
| Median (range) | 3 (1–6) | 3 (1–8) |
| $N$ obs. | 16 | 18 |
| Total | 53 | 61 |

$N$ obs., number observed.
[a] Another patient did not start treatment because of early death due to progressive disease (PD).

Table 3
Off-study reasons

| Variable | Treatment | | |
|---|---|---|---|
| | No hydration ($N=16$) $N$ (%) | Hydration ($N=18$)[a] $N$ (%) | Total ($N=34$) $N$ (%) |
| Major reason for discontinuation | | | |
| Progression of the disease | 13 (81) | 15 (83) | 28 (82) |
| Refusal of patient to continue | 0 | 1 (6) | 1 (3) |
| End of protocol treatment | 2 (13) | 2 (11) | 4 (12) |
| Major worsening of general status | 1 (6) | 0 | 1 (3) |

[a] Another patient did not start treatment because of early death due to progressive disease (PD).

Table 4
Efficacy outcome

| Variable | Treatment | | |
|---|---|---|---|
| | No hydration ($N=16$) $N$ (%) | Hydration ($N=19$) $N$ (%) | Total ($N=35$) $N$ (%) |
| Best overall response: consensus | | | |
| PR | 1 (6) | 1 (5) | 2 (6) |
| SD | 6 (38) | 5 (26) | 11 (31) |
| PD | 8 (50) | 10 (53) | 18 (51) |
| Early death due to malignant disease | 1 (6) | 1 (5) | 2 (6) |
| Not assessable | 0 | 1 (5) | 1 (3) |
| Patient did not get treatment | 0 | 1 (5) | 1 (3) |
| Response rate 95% CI: 2/34 = 5.9% (0.7–19.7%) | | | |

PR, partial response; SD, stable disease; 95% CI, 95% Confidence Interval.

The most common non-haematological treatment-related adverse events are shown in Table 6. They included fatigue (38% of patients experienced grade $\geqslant 2$), vomiting (33% grades 2 and 3) and renal, metabolic and electrolyte disturbances. Metabolic acidosis occurred in 2 patients both treated in the active-hydration arm, grade 3 hypokalaemia was observed in 3 cases during cycle 2 and in 2 others following cycles 5 and 6. Grade 3 hypophosphataemia was observed in 4 patients (3 in the hydration arm). Overall, 9 patients developed an increase in serum creatinine during treatment. 7 of those patients had been randomised to the active-hydration arm. In 2 cases, an increase to grade 2 and in 1 patient, a grade 4 serum creatinine increase was observed. In the 6 other patients, the creatinine increase was limited to grade 1. Most toxicities were resolved and chemotherapy with glufosfamide continued.

### 3.5. Pharmacokinetics

The overall performance of the analytical assay was acceptable as predefined precision criteria were met during an analysis of the test plasma samples. Plasma concentration–time profiles of glufosfamide were evaluated in 28 patients.

Summary pharmacokinetic data are shown in Table 7 and Fig. 2. The extrapolated $AUC^{\infty}$ was small and ranged between 2.1 and 11.2%. The median terminal elimination half-life ($t_{1/2}$) of glufosfamide was 1.88 h. As expected, $C_{max}$ (median 407.55, range 275.22–716.84 μg/ml) was observed at the end of the infusion time. The derived PK parameters showed moderate interindividual variability.

The plasma pharmacokinetics of i.v. infused glufosfamide, in this population of patients, was not influenced by hydration. Female patients seem to have a tendency for higher plasma concentrations and smaller CL values; however, the $t_{1/2}$ was not different. Patients who experienced any form of renal toxicity during the first chemotherapy cycle were not found to have different PK data from those that did not.

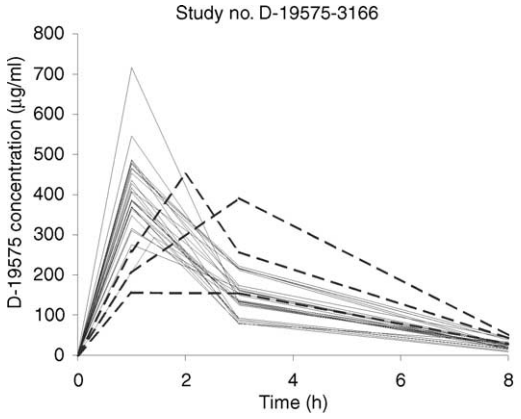


Fig. 2. Linear plot of the individual values of plasma concentration–time profiles of glufosfamide in patients in cycle 1 (dotted lines represent outliers in this array of curves).

Table 5
Haematological toxicity: haematological toxicities (nadir)—both arms

| Grade | 0 | 1 | 2 | 3 | 4 |
|---|---|---|---|---|---|
| Leucocytes | 15 (44) | 7 (21) | 7 (21) | 4 (12) | 1 (3) |
| Neutrophils | 28 (82) | – (–) | 1 (3) | 4 (12) | 1 (3) |
| Platelets | 29 (85) | 2 (6) | 1 (3) | 2 (6) | – (–) |
| Haemoglobin | 10 (29) | 11 (32) | 10 (29) | 3 (9) | – (–) |
| At least one haematological toxicity | 7 (21) | 8 (24) | 11 (32) | 7 (21) | 1 (3) |

## 4. Discussion

To date, only a limited number of pancreatic cancer patients have benefited from chemotherapy [21]. Therefore, it is suggested that patients with metastatic or unresectable pancreatic cancer should primarily be considered for participation in clinical studies to support the identification of new active therapies [10].

Pancreatic cancer can be considered as a potential indication for chemotherapy utilising glufosfamide as pancreatic tumour cells are characterised by having increased glycolysis and are reported to overexpress the

Table 6
Non-haematological toxicity: major non-haematological toxicities (worst *related* adverse event)

| Grade | 0 | 1 | 2 | 3 | 4 |
|---|---|---|---|---|---|
| Fatigue | 11 (32) | 5 (15) | 9 (26) | 3 (9) | 1 (3) |
| Acidosis | 29 (85) | – (–) | – (–) | 1 (3) | 1 (3) |
| Alopecia | 11 (32) | 15 (44) | 8 (24) | – (–) | – (–) |
| Diarrhoea | 28 (82) | 1 (3) | 2 (6) | 1 (3) | – (–) |
| Nausea | 9 (26) | 14 (41) | 10 (29) | 1 (3) | – (–) |
| Vomiting | 14 (41) | 9 (26) | 7 (21) | 4 (12) | – (–) |
| Haematuria | 30 (88) | 4 (12) | – (–) | – (–) | – (–) |
| proteinuria | 27 (79) | 3 (9) | 2 (6) | – (–) | – (–) |
| Hypokalaemia | 29 (85) | – (–) | – (–) | 5 (15) | – (–) |
| Hypophosphataemia | 30 (88) | – (–) | – (–) | 4 (12) | – (–) |

Table 7
Summary of pharmacokinetic data from 28 patients treated with 5 g/m$^2$ glufosfamide, tabulated by the hydration arm

| Arm | Statistical parameter | $C_{max}$ (μg/ml) | $t_{1/2}$ (h) | AUC (μg h/ml) | CL (ml/min/m$^2$) |
|---|---|---|---|---|---|
| Hydration | *N* | 14 | 13 | 13 | 13 |
| | Median | 426.60 | 1.85 | 1359.52 | 61.30 |
| Non-hydration | *N* | 14 | 14 | 14 | 14 |
| | Median | 386.15 | 1.91 | 1213.68 | 68.70 |

$t_{1/2}$, terminal elimination half-life; AUC, area under concentration curve; CL, clearance; $C_{max}$, maximum concentration.

glucose transporter system [14,22]. Preclinical findings suggest that cellular uptake of glufosfamide is mediated by a $Na^+$-dependent β-D-glucose transmembrane transporter (SAAT1) that is followed by intracellular enzymatic cleavage of the *O*-glycosidic bond and release of the isophosphoramide mustard (IPM) [15]. However, the results of the present phase II trial suggest that glufosfamide has modest activity against advanced/metastatic pancreatic adenocarcinoma. Glufosfamide treatment resulted in a 5.9% objective response rate, a stable disease rate of 32.4%, and a 5.3 months median overall duration of survival.

The antitumour activity of glufosfamide against pancreatic carcinoma at the studied dose and schedule still needs to be discussed before dismissing its efficacy. It is known that cytotoxic agents have limited activity in pancreatic cancer. Fluorouracil has been extensively studied as a single agent or in a variety of combinations, with objective response rates ranging from 20% to zero in more recent studies [5,23,24]. Other agents that demonstrate activity include cisplatin, docetaxel and gemcitabine [25–27]. Gemcitabine has been shown to be superior to 5-FU (bolus) with respect to clinical benefit in a randomised phase II trial [5]. In another trial single agent gemcitabine demonstrated partial remission in 2/32 patients and disease stabilisation in 6/32 patients [27]. The response rate and the duration of survival achieved with glufosfamide are comparable with published results of single agent chemotherapy of pancreatic cancer with gemcitabine. It must be mentioned that the clinical benefit response (including the parameters of decreased pain, reduced intake of analgesics, increased performance status, and weight gain) was not assessed in the present glufosfamide trial.

Acute myelotoxicity was particularly mild in the present trial. However, renal toxicity was observed and confirms the dose-limiting toxicity described in the phase I studies [11]. No nephroprotective effect was observed in patients allocated to the active-hydration arm compared with the non-active-hydration arm. Therefore, as assessed in this small patient population, forced hydration did not offer any nephroprotective effect towards glufosfamide by reducing the contact time of tubule cells with the drug. The plasma pharmacokinetics of i.v. infused glufosfamide in patients with advanced pancreatic cancer was not influenced by hydration. There was also no evidence of a relationship between PK data and the occurrence of renal toxicity.

We conclude that glufosfamide has a modest antitumoral activity as a first-line treatment in pancreatic cancer. It has comparable antitumour activity to other cytotoxic agents registered for this indication.

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