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A multinational phase 2 study of nanoliposomal irinotecan sucrosfate (PEP02, MM-398) for patients with gemcitabine-refractory metastatic pancreatic cancer

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Background: PEP02, also known as MM-398, is a novel nanoliposomal irinotecan that has improved pharmacokinetics and tumour bio-distribution of the free drug. This phase 2 study evaluated PEP02 monotherapy as second-line treatment for pancreatic cancer.

Methods: Patients who had metastatic pancreatic adenocarcinoma, Karnofsky performance status ≥ 70 , and had progressed following gemcitabine-based therapy were eligible. Intravenous injection of PEP02 120 mg m⁻² was given every 3 weeks. Simon 2-stage design was used. The primary objective was 3-month survival rate (OS_{3-month}).

Results: A total of 40 patients were enrolled. The most common severe adverse events included neutropenia, abdominal pain, asthenia, and diarrhoea. Three patients (7.5%) achieved an objective response, with an additional 17 (42.5%) demonstrating stable disease for a minimum of two cycles. Ten (31.3%) of 32 patients with an elevated baseline CA19-9 had a >50% biomarker decline. The study met its primary end point with an OS_{3-month} of 75%, with median progression-free survival and overall survival of 2.4 and 5.2 months, respectively.

Conclusion: PEP02 demonstrates moderate antitumour activity with a manageable side effect profile for metastatic, gemcitabine-refractory pancreatic cancer patients. Given the limited treatment options available to this patient population, a phase 3 trial of PEP02 (MM-398), referred to as NAPOLI-1, is currently underway.

Therapeutic options for patients with advanced pancreatic cancer (APC) range from gemcitabine monotherapy to multiple-drug regimens, depending on age, performance status, comorbid conditions, and patient and physician preference. Recently, results

of a phase 3 clinical trial from France (PRODIGE 4/ACCORD 11) demonstrated the superiority of FOLFIRINOX (biweekly infusional 5-fluorouracil, leucovorin, irinotecan, and oxaliplatin) over gemcitabine in the first-line treatment of metastatic pancreatic

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cancer, with improvements in response rate, progression-free survival, and overall survival, albeit with greater toxicity (Conroy *et al*, 2011).

Beyond first-line therapy, options for metastatic pancreatic cancer become less clear, as patients often demonstrate rapid clinical deterioration and are no longer suitable candidates for additional treatment beyond best supportive care. One co-operative group trial reported that only 45% of patients with APC went on to receive additional therapy following progression on front-line study treatment (Schrug *et al*, 2007). A number of small prospective single-arm studies have evaluated both cytotoxic and/or targeted agents in the setting of gemcitabine-refractory disease, generally demonstrating low response rates and progression-free survival of a few months at best (Burris *et al*, 2005; Boeck *et al*, 2007; Kulke *et al*, 2007; Ko *et al*, 2008, 2010; Oh *et al*, 2010; O'Reilly *et al*, 2010). Results from a randomised German trial for the second-line treatment of APC (CONKO-003) suggested a weekly regimen called OFF (oxaliplatin, 5-FU given as a 24-hour infusion, and folinic acid) may improve patient outcomes in patients refractory to gemcitabine (Pelzer *et al*, 2008, 2011). At present, however, there is no recognised standard of care in this setting.

PEP02 (also known as MM-398) is irinotecan sucrosfate encapsulated in a liposome drug delivery system. This stable nanoliposomal formulation has been shown in preclinical studies to improve pharmacokinetics and tumour bio-distribution of both irinotecan and its active metabolite SN-38 when compared with the free form of the drug, with less accumulation in many of the target organs associated with toxic side effects. PEP02 also demonstrated increased efficacy and tolerable toxicity when compared with free irinotecan in an orthotopic pancreatic cancer mouse model (Hann *et al*, 2007). The favourable pharmacokinetics of irinotecan and SN-38 after PEP02 was confirmed in the first-in-human phase 1 trial for refractory solid tumours, in which the maximum tolerated dose of PEP02 given every 3 weeks was determined as 120 mg m^{-2} (Chen *et al*, 2008). This non-randomised phase 2 trial, conducted in the United States and Taiwan, sought to establish the efficacy and toxicity of single-agent PEP02 in patients with metastatic pancreatic cancer after progression on first-line gemcitabine-based therapy.

PATIENTS AND METHODS

Trial design and patients. This trial was an international, multicenter, open-label, phase 2 study of PEP02 (liposome encapsulated irinotecan, PharmaEngine Inc, Taipei, Taiwan) in patients with gemcitabine-based chemotherapy failure metastatic pancreatic adenocarcinoma.

Patients with histologically confirmed adenocarcinoma of the exocrine pancreas refractory to gemcitabine-based (either alone or in combination) systemic chemotherapy, including those with disease progression within 6 months after post operative adjuvant therapy, were eligible. Prior treatment with irinotecan was not allowed. Further inclusion criteria were age ≥ 18 years, Karnofsky performance status of ≥ 50 (subsequently amended to ≥ 70 to ensure patient safety and to be consistent with the eligibility criteria of other clinical trials for this same patient population), with extrapancreatic metastases diagnosed either radiographically or by biopsy confirmation, and adequate bone marrow and hepatic functions within 1 week before commencing treatment (absolute neutrophil count $\geq 1.5 \times 10^3 \text{ ml}^{-1}$, platelets $\geq 100 \times 10^3 \text{ ml}^{-1}$, serum bilirubin within upper limit of normal (ULN), transaminase $\leq 2.5 \times \text{ULN}$ ($\leq 5 \times \text{ULN}$ in patients with liver metastases). All prior major surgery, radiotherapy (except palliative), or investigational drug therapy, had to be ceased at least 4 weeks and all treatment-related toxicities had to be resolved to no greater than grade 1 before enrolment. Patients with central nervous system

metastases, pregnancy, uncontrolled active infection, another primary malignancy within the past 5 years except curatively treated non-melanoma skin cancer or cervical carcinoma *in situ*, or other concomitant serious diseases, were excluded.

All patients gave written informed consent. The trial was approved by the independent ethics committee of each participating institute, and performed in accordance with the International Conference on Harmonization Good Clinical Practice guidelines, Good Clinical Laboratory Practice, and the Declaration of Helsinki. The trial was also registered with clinical trials.gov identifier NCT00813163.

Treatment and assessments. PEP02 at a dose of 120 mg m^{-2} was diluted in 500 ml of 5% dextrose and delivered as a 90-min intravenous infusion every 21 days. Infusion time was allowed to be prolonged for acute infusion-associated reactions or any other clinical needs. Premedication included dexamethasone and a serotonin antagonist. Prophylactic anticholinergic agent was not given unless an acute cholinergic reaction was observed during a prior cycle of treatment. Imodium, growth factor support, and anticoagulation (warfarin or low-molecular heparin) were allowable per protocol as clinically indicated, but not for primary prophylaxis. Detailed history evaluation, vital signs recording, physical examination, complete blood count with differential classification, and blood biochemistry tests were performed weekly during the first treatment cycle and before the start of each treatment cycle thereafter. Toxicity was recorded according to the National Cancer Institute-Common Toxicity Criteria (NCI-CTC) version 3.0.

Dose adjustments in PEP02 were made according to toxicities observed with each treatment cycle. The protocol allowed, at the discretion of the treating physician, escalation of PEP02 to 150 mg m^{-2} beginning with cycle no. 2 in patients who did not experience drug-related toxicities worse than grade 1. The development of grade 3 or 4 diarrhoea, grade 4 or febrile neutropenia, or any other grade 3 or 4 toxicity required a dose reduction of study drug in 20 mg m^{-2} decrements, to a lowest dose level permissible of 80 mg m^{-2} , with no subsequent dose re-escalation allowed. The treatment was continued until evidence of disease progression, unacceptable toxicity, treatment delay for > 2 weeks, patient withdrawal of consent, or death.

Imaging studies, preferably using computed tomography, were performed at baseline and after every two cycles of chemotherapy to evaluate tumour response, which was determined according to the RECIST version 1.0 guidelines. All complete and partial responses required confirmation by two consecutive observations no less than 4 weeks apart. CA19-9 was measured before each cycle of treatment, and CA19-9 tumour marker response (defined as a decrease of $\geq 50\%$ of CA 19-9 in relation to baseline level at least once during the treatment period, in patients with baseline values above the ULN) was determined. Patient diaries were dispensed to collect pain information (including pain intensity and morphine consumption). Patients' survival status was tracked at the 90th day after the start of PEP02 treatment (cycle 1, day 1) and every 2 months after withdrawal. The date of death was recorded.

Statistical analysis. The primary end point of this study was 3-month survival rate ($\text{OS}_{3\text{-month}}$). Secondary end points included other clinical efficacy variables (objective tumour response, progression-free and overall survival, clinical benefit response (as defined in Burris *et al*, 1997), CA19-9 tumour marker response), and safety profile. A randomised phase 3 trial by the German CONKO-study group (Pelzer *et al*, 2011) reported a median survival of 2.3 months in patients receiving best supportive care after front-line gemcitabine-based therapy, with a $\text{OS}_{3\text{-month}}$ of $\sim 35\%$. Thus, for the current study, we used as the null hypothesis (H_0) and alternative hypothesis (H_a) a $\text{OS}_{3\text{-month}}$ of 40% and 65%, respectively. The study used an optimal Simon 2-stage design.

With a significance level of $\alpha = 0.05$ and a type 2 error $\beta = 0.10$, if 8 of the first 16 patients enrolled in the first stage reached the 3-month survival time-point, an additional 23 patients would be enrolled in the second stage. At least 21 of the 39 patients were required to survive 3 months or longer to allow rejection of the null hypothesis. A safety stopping rule would be invoked if six or more patients in the first stage experienced grade 3 or 4 diarrhoea.

Descriptive statistics were used for all efficacy variables, with the primary analysis population being the per protocol population (defined as study participants who met all inclusion/exclusion criteria and did not significantly deviate from the study protocol). The frequencies of patients with adverse events were summarised by body system and by major adverse event codes (system/organ/class).

RESULTS

Patient characteristics. Baseline patient characteristics are shown in Table 1. A total of 40 patients were enrolled for the study between March 2009 and September 2010, with an approximately even distribution between US and Taiwanese sites. The majority of patients (60%) had a Karnofsky Performance Score of 90–100 and 77.5% had received a prior gemcitabine-based combination, as opposed to monotherapy, as their first-line regimen. The duration of front-line therapy ranged from 1 to 24 months.

Drug delivery and adverse events. Patients received a mean of 5.875 treatment cycles (range, 1–28 cycles; median 2.5 cycles). Owing to concerns of excess toxicity, primarily asthenia, observed in US patients at the starting dose of 120 mg m^{-2} , the protocol was

subsequently amended during the second stage of the study to permit a lower starting dose at 100 mg m^{-2} . In total, 27 of 40 patients (67.5%) on the study were able to be maintained at a dose of 120 mg m^{-2} throughout their entire treatment course, whereas 11 (27.5%) required or initiated therapy at reduced doses. Eleven patients (27.5%) received at least eight treatment cycles. The majority of patients (75%) discontinued study treatment due to disease progression.

The most common toxicities observed during study treatment are shown in Table 2. As expected, gastrointestinal and haematologic toxicities were the most common types seen, as well as fatigue and abdominal pain; these latter symptoms may have been related either to study treatment or to the underlying cancer. In total, 26 patients (65%) experienced at least one treatment-emergent adverse event categorised as grade 3 or higher. Of note, six patients died within 30 days of the last dose of study treatment. Of these, three were attributed to disease progression; the other three were due to respiratory failure, aspiration pneumonia, and sepsis, all in the setting of neutropenia.

Efficacy. Efficacy results are shown in Table 3. Half of the patients (50%) had evidence of disease control (objective response plus stable disease for more than two cycles), including three patients (7.5%) who achieved a confirmed objective response. Fourteen of the 17 patients with stable disease as their best response demonstrated disease stability for at least four cycles (35% of the entire cohort). A waterfall plot (Figure 1) demonstrates best

Table 1. Patient demographics and baseline characteristics

Characteristic	n = 40
Sex, n (%)	
Male/female	19 (47.5)/21 (52.5)
Age, mean (range) years	58.8 (39–82)
Study site, n (%)	
Taiwan/USA	22 (55)/18 (45)
Ethnicity, n (%)	
Asian/Caucasian	25 (62.5)/15 (37.5)
Karnofsky performance status, n (%)	
100	7 (17.5)
90	17 (42.5)
80	6 (15.0)
70	10 (25.0)
Prior treatment, n (%)	
Chemotherapy	40 (100)
Radiotherapy	10 (25.0)
Surgery	17 (42.5)
First-line chemotherapy and duration in months	
Gemcitabine monotherapy, n (%) / median (range)	9 (22.5) / 2 (1.5–24)
Gemcitabine-based combination, n (%) / median (range)	31 (77.5) / 6 (1–16)
With elevated CA19-9, n	32
Baseline clinical benefit parameters, n (%)	
Pain intensity ≥ 20 (out of 100)	17 (42.5)
Morphine consumption $\geq 10 \text{ mg per day}$	14 (35.0)

Table 2. (A) Treatment-emergent adverse events (all grades) occurring in 10% or greater of study patients. (B) Treatment-emergent grades 3–4 adverse events occurring in 10% or greater of study patients

A	
Adverse event, all grades	N (%)
Diarrhoea	30 (75%)
Fatigue	25 (62.5%)
Nausea	24 (60%)
Anorexia	23 (57.5%)
Vomiting	23 (57.5%)
Alopecia	17 (42.5%)
Neutropenia	16 (40%)
Leucopenia	15 (37.5%)
Abdominal pain	15 (37.5%)
Weight decreased	15 (37.5%)
Anaemia	13 (32.5%)
B	
Adverse event, grades 3–4	N (%)
Neutropenia	12 (30%)
Leucopenia	10 (25%)
Abdominal pain	6 (15%)
Fatigue/asthenia	8 (20%)
Anaemia	6 (15%)
Hyponatremia	6 (15%)
Diarrhoea	6 (15%)
GGT elevated	5 (12.5%)
Anorexia	4 (10%)
Nausea	4 (10%)

Table 3. Efficacy data

Best tumour response (n = 40)		N (%)
Partial response		3 (7.5%)
Stable disease		17 (42.5%) ^a
Disease Progression		10 (25.0%)
Non-evaluable ^b		10 (25.0%)
Disease control (PR + SD) rate		20 (50.0%)
Survival		Months
Progression-free survival (median)		2.4
Overall survival (median)		5.2
Proportion of patients alive at:		N (%)
Three months		30 (75%)
Six months		17 (42.5%)
Twelve months		10 (25%)
Clinical benefit response (n = 25 evaluable)		5 (20%)
CA19-9 decline > 50% (n = 32 with elevated level at baseline)		10 (31.3%)

Abbreviations: PR = partial response; SD = Stable disease.
^aIncluding eight patients with minor response.
^bNon-evaluable patients for tumor response included those patients with non-measurable disease at baseline or in whom at least one post treatment radiographic evaluation was not performed.

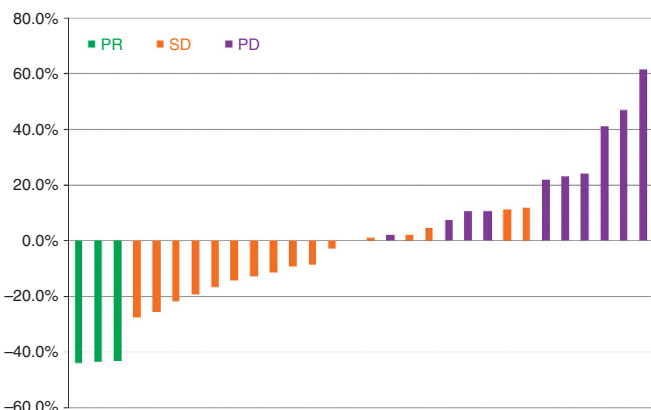


Figure 1. Maximum % change from baseline in sum of target lesion diameters (evaluable patients only, n = 30). Abbreviations: PD = disease progression; PR = partial response; SD = stable disease.

tumour response observed in evaluable study patients. Ten (31.3%) of 32 patients with elevated baseline CA19-9 had > 50% biomarker decline, and 5 (20%) of 25 CBR-evaluable patients achieved significant clinical benefit. Median progression-free and overall survival was 2.4 and 5.2 months, respectively (Figure 2). These indicators of antitumour activity are also listed in Table 3. Notably, the study met its primary end point with 75% of patients surviving at least 3 months, including 25% reaching the 1-year mark. Two patients were still alive as of July 2012. Survival outcomes for patients receiving PEP02 showed a modest positive correlation with the duration of prior gemcitabine-based therapy (Figure 3).

DISCUSSION

There is a relative paucity of published studies evaluating the safety and efficacy of chemotherapy regimens in patients with APC who have progressed following first-line therapy. An inherent selection

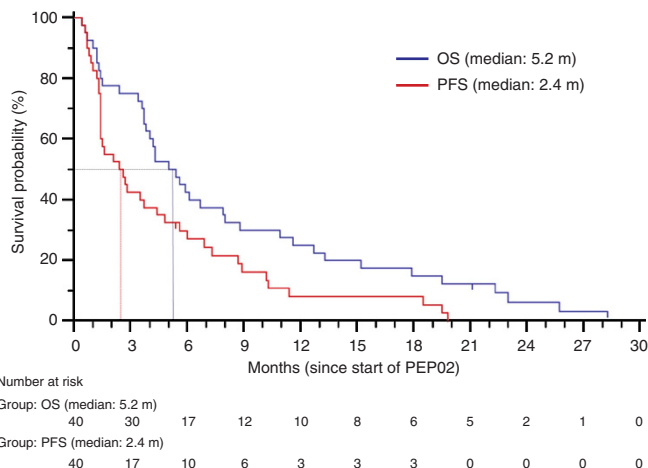


Figure 2. Kaplan–Meier curves of overall and progression-free survival. Abbreviations: m = months; OS = overall survival; PFS = progression-free survival.

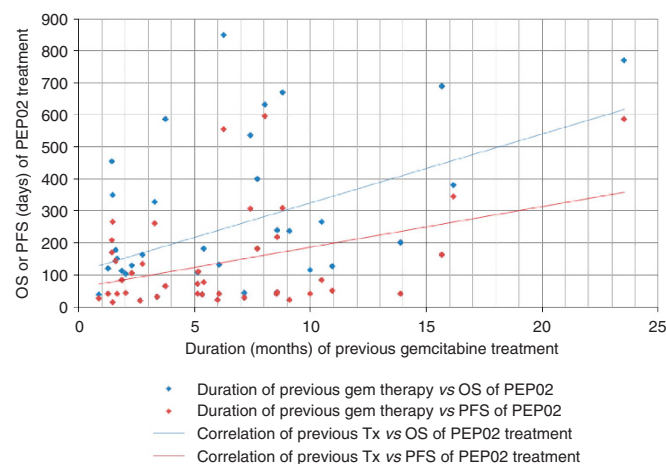


Figure 3. Overall survival (OS) and progression-free survival (PFS) relative to the duration of prior gemcitabine-based therapy. Abbreviations: Gem = gemcitabine; Tx = treatment.

bias is at work in non-randomised trials, as those patients who are well enough to consider salvage treatment may have more favourable tumour biology and a longer survival independent of choice of therapy. Conversely, design of a randomised study in this setting is challenging due to lack of agreement regarding the appropriate selection of control arm; a comparator arm of best supportive care alone, although perhaps appropriate in many cases, is not an appealing option to patients. Results from one of the largest studies conducted to date for the second-line treatment of APC (CONKO-003) randomised 165 patients to receive a weekly regimen called OFF or 5-FU/folinic acid alone (Pelzer *et al*, 2008). Patients receiving the oxaliplatin-containing combination demonstrated significantly improved outcomes in terms of both progression-free survival (13 vs 9 weeks, $P=0.012$) and overall survival (26 vs 13 weeks, $P=0.014$), leading to the adoption of this regimen (or slight variations thereof) as a *de facto* standard of care in the salvage setting.

Irinotecan is a topoisomerase 1 inhibitor that is currently used to treat the colorectal, gastric, lung, uterine, cervical, and ovarian cancers. At higher doses, the drug causes severe diarrhoea and myelosuppression, which is recognised as its dose-limiting toxicity. Specific to pancreatic cancer, irinotecan represents a component of the FOLFIRINOX regimen that has recently demonstrated superior activity to gemcitabine in the front-line setting (Conroy *et al*,

2011), and has also been evaluated as part of combination regimens for refractory disease in several studies (Ko *et al*, 2008; Yoo *et al*, 2009; Gebbia *et al*, 2010; Oh *et al*, 2010; Assaf *et al*, 2011; Zaniboni *et al*, 2012). A recently reported phase 2 trial performed by the Italian Group for the Study of Gastrointestinal Tract Cancer (GISCAD) showed that FOLFIRI produced median progression-free and overall survival rates of 3.2 and 5 months, respectively, in the second-line treatment of APC (Zaniboni *et al*, 2012).

PEP02 is irinotecan encapsulated in a liposome drug delivery system. Liposome drug formulations may reduce the toxicity of an encapsulated agent to healthy tissue while maintaining, or increasing, its antitumour potency. The therapeutic benefits of liposome encapsulated anticancer drugs such as daunorubicin, doxorubicin, and cytarabine are well-established. Preclinical *in vivo* efficacy data have shown improved antitumour activity of PEP02 over the equivalent dose of free irinotecan in multiple established human tumour xenograft mouse models, including brain, colon, and pancreatic cancers (Hann *et al*, 2007). In previous phase 1 studies, PEP02 either alone or in combination with 5-FU/leucovorin demonstrated prolonged disease control in five of seven (71%) patients with gemcitabine-refractory APC (Chen *et al*, 2008, 2010).

On these bases, the current non-randomised phase 2 trial was conducted to establish the preliminary efficacy and safety of PEP02 in the second-line setting for patients with metastatic pancreatic cancer. Recognising the aforementioned limitations that accompany a single-arm study design, PEP02 did show clear evidence of antitumour activity in a subset of patients in whom no standard of care therapy otherwise exists. In addition, although its efficacy profile appears similar to that seen with FOLFIRI in the GISCAD trial for the same patient population, PEP02 may offer advantages in its relative ease of administration as monotherapy without the requirement of an infusion pump. However, it should also be acknowledged that although PEP02 was generally well-tolerated in most patients, with manageable and predictable toxicities, the majority of subjects did experience at least one grade 3 or higher adverse event. In addition, there were three patient deaths that occurred within 30 days of the last dose of study treatment relating to complications of neutropenia. These findings highlight the need to be particularly vigilant with PEP02 (or any cytotoxic therapy, for that matter) in such a fragile patient population, and may support the use of preemptive growth factor support in select patients. Pharmacogenetic testing for polymorphisms in genes relating to the metabolism of PEP02, including UGT1A1 and UGT1A9, was performed on 28 patients; no correlation with either haematologic or non-haematologic toxicity was observed (data not shown).

Although analysis of germline polymorphisms from peripheral blood samples was possible on all study patients, there were not adequate tumour tissue samples available to look for intratumoural molecular biomarkers of potential predictive significance. Such correlative studies represent one of the 'holy grails' that are often attempted to be embedded within pancreatic cancer clinical trials; however, due to scant archived samples and the difficulties in subjecting this patient population to prospective tissue biopsies for research purposes, they continue to present a tremendous challenge in this disease. This obstacle is magnified all the more so in the salvage treatment setting.

The results of this clinical trial are encouraging enough to warrant moving ahead with a larger study in a similar patient population, currently ongoing as an international randomised phase 3 trial called NAPOLI-1 (clinicaltrials.gov. ID: NCT01494506, EudraCT Number: 2011-004687-30). Additional studies may explore this drug's potential role in the first-line setting and as part of combination regimens for APC. Moreover, given the emergence of FOLFIRINOX as a front-line standard in patients with good performance status, the utility of PEP02 in irinotecan-pretreated patients, alone or in combination with gemcitabine, also merits further investigation.

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CONFLICT OF INTEREST

LTC is a consultant and has received honorarium from PharmaEngine. CGY and YWW are employees and hold stock of PharmaEngine, the makers of PEP02. AHK, MAT, YSS, WCS, YLL, ED and AO declares no conflict of interest.

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