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Phase II Study of EUS-guided Verteporfin PDT in Solid Pancreatic Tumors (VERTPAC-02)

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Phase II study of EUS-guided verteporfin PDT in solid pancreatic tumors (VERTPAC-02)

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SUMMARY OF PROJECT 2 SUPPLMENT (06/2015)

The goal of project 2 is to transform the management of pancreatic cancer (PanCa), a devastating disease that is most often diagnosed in later stages, when curative therapies are unlikely. This strategy starts with a target of advanced or locally advanced pancreatic cancer (LAPC) with a phase II trial of photodynamic therapy (PDT) to evaluate local destruction of the tumor. This is later followed by a combination therapy of PDT and MM398, as a secondary goal of treating metastatic disease. This initial Phase II trial is the stepping stone towards the more needed combination therapy trial, which has the potential of seriously impacting long term survival of these patients. ***As such, we are proposing to expedite the Phase 2 by creation of a multi-center trial, combining patients at the University College London Hospital with a new two sites in the Mayo Clinic Health System (Rochester, MN). This approach should increase the recruitment rate, and lead to a faster completion, allowing earlier transition to the combination therapy trial, and also brings part of the study to the United States for evaluation here.*** This trial will utilize a minimally invasive approach of endoscopic ultrasound (EUS)-guided PDT, with the goal for outpatient therapy with improved safety and healthcare costs. Together, the UCLH and Mayo clinic will establish, in a multicenter phase II study, the efficacy of EUS-PDT using verteporfin (benzoporphyrin, BPD) to ablate solid tumors of the pancreas. Clinical contrast CT-based treatment planning will be used to deliver patient-specific PDT in the trial as well, adding additional dosimetry innovation to the study. The study will recruit both localize advanced pancreatic cancer and metastatic disease, that will also establish the safety of giving chemotherapy almost immediately after PDT. The immediate impact of this project will be to improve the care of patients with PanCa, and more broadly the findings will establish a clinical framework to translate new nanomedicine and combination-based targeted therapeutic discoveries for cancer.

Potential public health benefits: The clinical studies described above provide new minimally invasive treatment option aimed at improving the length and quality of life in patients with PanCa. Rapid control of local disease can help alleviate obstructive symptoms and increase tolerance to systemic therapy. The multi-center approach to the trial will bring the treatment to the United States for evaluation in our healthcare system, as well as expedite the results of the trial, to allow the eventual combination trial to be completed in a more efficient manner.

SPECIFIC AIMS

The overall aim of this supplement is to contribute to improved treatment of pancreatic tumors, using the minimally invasive technique of endoscopic ultrasound (EUS)-guided PDT and CT-based dosimetry as a predictive tool for treatment planning, which was shown to be a key element in this program project. The five-year survival of PanCa is less than 6% and this has remained unchanged over the last four decades. This work follows on from the PI, Dr,Pereira's recently completed phase I clinical study of verteporfin PDT in patients with PanCa. In this dose escalation study, it was demonstrated that PDT can be delivered safely to patients with locally advanced cancers, with an increase in the diameter of necrosis with increasing light dose. The phase II proposed follow up will confirm that beyond safety, that PDT can yield good local control of pancreas disease. These studies will then inform the design of future studies of PDT + advanced chemotherapy combinations, as proposed in the last aim of the Project 2. The primary goal of this supplemental study is to assist the Phase 2 recruitment and trial by doubling the number of subjects that can be recruited, and power the study to assess

Hypothesis 1: EUS-guided PDT will provide effective ablation of solid lesions of the pancreas (multi-center phase II clinical trial at UCL + Mayo).

Clinical use of PDT for PanCa has been pioneered by the Project 2 group, and a positive correlation was established between delivered energy and the extent of tumor necrosis around interstitial fibers, with no serious adverse events. We aim to improve the approach by moving to a minimally invasive approach of EUS, in conjunction with dosimetry to monitor treatment (jointly with *Project 4*).

Aim 1. To participate in the conduct a phase II study of EUS-guided PDT in PanCa. PDT will be done initially at a single site with a fixed light dose for the first group of patients, then at multiple sites to match the zone of tumor necrosis to tumor volume.

This work will lead into the next logical step in the trial, which was the major goal of Project 2, namely a combination therapy trial using PDT, standard chemotherapy and in patients with advanced or locally advanced and metastatic disease. The advanced cancer patients will be defined as patients with at least a 50% increase in tumor volume or new metastasis regardless of whether the patients had chemotherapy. All participants will be within ECOG performance status of 0-2.This work provides a direct bench-to-bedside translation, as we will use the most effective combination sequence form project 3 as they study in pre-clinical work. While this is not the goal of this current supplement, it is a future direction, which will be expedited by the completion of this proposed Phase II trial.

After intravenous administration of verteporfin, fluorescence readings will be taken from the patient's buccal mucosa to register the fluorescence peak. This is performed using a mobile fluorimeter that using an ipad as the processor. The device delivers a very small amount of light to the buccal mucosal and can measure nanogram levels of drugs. A gradient spectrophotometer is coupled to a CCD to record the fluorescence. Background fluorescence will be performed earlier in the day from the same area of buccal mucosa. The measurements will be taken every 10 minutes until the procedure (total 6-9 measurements).

We plan to take FNA biopsies of the lymphocytes to assess immune response due to treatment.

Research Strategy

a) SIGNIFICANCE

The goal of this project is to transform the management of pancreatic cancer (PanCa) in the advanced or locally advanced, and metastatic phases, using PDT in combination with systemic therapy. Specifically, we will build on our previous phase I findings of PDT-induced tumor necrosis in PanCa patients that has been shown to be safe without significant toxicities, and move to the minimally invasive approach of EUS-guided PDT, with the potential for outpatient therapy with improved safety and healthcare costs. Prior studies in a mouse xenogaft model of pancreatic cancer at the Mayo Clinic also demonstrated the potential efficacy of next generation photosensitizers in photodynamic therapy. In particular, given that most pancreatic cancers consist of fibroblasts that encase tumor cells, it appears logically to have a locally delivered therapy which could potentiate additional chemotherapeutic agents. We will allow early delivery of chemotherapy after this therapy and observe if this can enhance the effectiveness of chemotherapy. Single therapies alone are ineffective in PanCa, it is hypothesized that this combination strategy will enhance survival of patients who have advanced or locally advanced and/or metastatic disease. We will also use EUS-PDT in patients with premalignant cystic neoplasms of the pancreas, which carry a significant risk of cancer development.

a.1: Pancreatic Cancer

Worldwide, PanCa is one of the top 10 leading causes of cancer deaths, and ranks fourth as a cause of cancer death in the UK and USA (1). Overall, the long term prognosis of the disease is poor with a one-year survival rate of no more than 10%. For cancers staged more advanced than Stage 1B, 5 year survival in less than 7%. For non-metastatic disease, median survival is 6–10 months although for those with metastatic disease at presentation, survival is only 3–6 months (2, 3). While there have been small gains in therapeutic options for patients in recent years, there has been no significant improvement in overall outcome for more than two decades. Novel treatment strategies for advanced tumors and improved detection and ablation of premalignant lesions are necessary to improve outcome.

According to the SEER (Surveillance, Epidemiology, and End Results Program) database, it is projected that there will be 48,760 new cases of pancreatic cancers in the United States (incidence of 10.4/100,000) with a five year projected survival rate of only 7.2%. The lifetime risk of developing pancreatic cancer is 1.5% in both men and women. There is also estimated to be 40,560 deaths due to pancreatic cancers in 2015. There has not been a major advancement in survival with unresectable pancreatic cancer that is the primary rationale for the development of new innovative therapies such as photodynamic therapy.

a.2: Current treatment of pancreatic cancer

In series from specialized centers, over 10% of patients may be resectable at presentation, but in larger population-based studies the number undergoing resection with curative intent may be as low as 3% (4, 5). Even after resection, median survival is only 10–20 months and no more than 5–20% of resected patients survive more than five years (6). Options available for the treatment of inoperable patients are largely limited to chemotherapy, radiotherapy, or some combination of the two. In both the US and Europe, gemcitabine is the most commonly used agent. The UK GemCap study - a phase III multicenter randomized clinical trial comparing gemcitabine alone or in combination with capecitabine for the treatment of 533 patients with advanced PanCa – reported a median survival in the combination capecitabine + gemcitabine group of 7.1 months compared with 6.2 months in those who received gemcitabine alone, with 1-year overall survival rates of 24.3% vs 22% (HR = 0.86; P=0.077) (7). The French randomized study of FOLFIRINOX (fluorouracil, leucovorin, irinotecan and oxaliplatin) versus gemcitabine chemotherapy, showed a significantly improved survival in the FOLFIRINOX group (median 11.1 vs 6.8 months; hazard ratio [HR] = 0.57; P<0.001)) (8). A phase III study of weekly intravenous albumin-bound paclitaxel (nab-paclitaxel) plus gemcitabine resulted in a significantly higher overall survival compared with gemcitabine monotherapy (8.5 vs 6.7 months; HR = 0.72; P<0.001), with survival rates of 35% versus 22% at 1 year (9). Further studies into combination regimens are needed. Trials of biological agents such as VEGF inhibitors in advanced disease have been largely unsatisfactory (10). The Canadian phase III trial of gemcitabine with erlotinib (a small molecule EGFR inhibitor) compared to gemcitabine alone, showed a significantly improved overall

survival in the combination arm, albeit with a median survival of only 6.2 vs. 5.9 months (11). Overall, the long-term prognosis of the disease is poor. Given these dismal results, surgical debulking or interstitial ablation has been investigated as a potential additional therapy in PanCa. In a recent systematic review comparing R2 resections to palliative bypass alone in the management of advanced pancreatic ductal adenocarcinoma (PDAC), a small non-significant survival advantage was observed in the R2 resection group; 8.2 months compared to 6.7 months in the palliative bypass group. However patients undergoing R2 resections had a significantly higher morbidity (RR: 1.75, 95% CI 1.35–2.26; P<0.0001), mortality (RR: 2.98, 95% CI 1.31–6.75; P=0.009) and a longer hospital stay (mean difference, 5 days; 95% CI 1–9 days; P=0.02), so that R2 resections cannot be recommended as part of standard management (12). In considering better alternatives, minimally invasive ablative therapies delivered percutaneously or endoscopically have become part of standard therapy in many other solid organ tumors, particularly in patients with inoperable disease or in patients unfit for surgical resection.(13) We therefore believe that for PanCa, a minimally invasive treatment capable of local destruction of tumor tissue with low morbidity may have an important place in the treatment of this disease.

a.3. Future treatment: Advantages of Endoscopic versus Percutaneous delivery of PDT for PanCa

PDT is a targeted anti-cancer treatment modality that has been extensively investigated in preclinical PanCa models by our group for mTHPC (14) and verteporfin (15) mediated PDT. These studies showed safety and efficacy in both normal tissues and transplanted tumors. We have also performed initial clinical studies of PDT for PanCa using mTHPC and CT-guided, percutaneous needle placement. Our group has showed feasibility, safety to surrounding normal tissues and successful induction of tumor necrosis; indicating that PDT was useful for local debulking of PanCa (16). These results motivated a Phase I clinical study using verteporfin-mediated PDT - chosen over mTHPC due to a reduced drug-light interval and photosensitivity times. We will develop a similar protocol for EUS-guided PDT of cystic tumors of the pancreas. Based on our own published experience with endoscopic PDT and EUS-FNA (17, 18), we expect EUS-PDT to be associated with a very low side effect profile and fewer complications than interstitial PDT or EUS-guided alcohol injection or radiofrequency ablation and will be an ideal therapy for those who are unfit for surgery or who have premalignant lesions who would otherwise require long-term surveillance. EUS-PDT represents a highly innovative approach towards day case anticancer therapy.

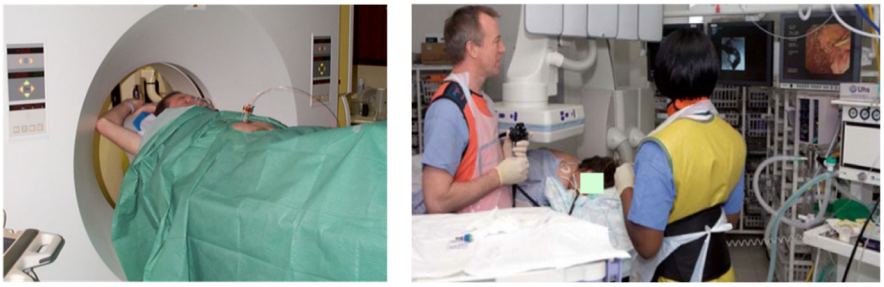

Fig. 1. a) Light delivery after CT-guided insertion of multiple 19G needles into the pancreas under local anaesthetic and i.v. sedation. **b)** Endoscopic delivery of PDT under conscious sedation.

a.5: Experimental Treatments for Locally Advanced Pancreatic Cancer at the Mayo Clinic

The Mayo Clinic currently is the site of a Pancreatic Cancer SPORE headed by Gloria Petersen, PhD. The institution has been very active in the development of potential therapies for pancreatic cancer. Several recent studies have involved potential new therapeutic pathways. This includes a recently published study investigating the use of inhibitors of Nampt to decrease pancreatic cancer cell growth in vitro and in vivo animal models. This is a novel approach that targets the NAD salvage synthesis pathway and inhibition of Nampt was found to decrease lactate production, mitochondrial function, and ATP. In addition, CD38 which is an NADase was found to modulate this effect. Lowering the level of CD38 decreased the response of Nampt to inhibition which was a novel observation. This pathway might well enhance the effects of PDT on pancreatic cancer (57). Mayo Clinic researchers also recently published on the advantages of the combined effects of TRAIL and GSK-3 inhibitors on increasing apoptosis in pancreatic cancer cell lines resistant to apoptosis. These investigators found that overexpression of GSK-3B led to resistance to pro-apoptotic signaling from TNFa and TRAIL through anti-apoptotic genes such as Bcl-xL. This was reversed by inhibition of GSK-3B. These observations lend further rationale to the addition of GSK-3 inhibitors to TRAIL for therapy of pancreatic cancer (58). These are only a sample of the studies that have been developed through our Pancreatic Cancer Spore.

Efforts have also been made to characterize young onset pancreatic cancer in a study being conducted at the Mayo Clinic that is collecting genetic information on all patients with pancreatic cancer diagnosed earlier than age fifty. It is hoped that specific genetic patterns can be detected to determine if there are underlying mechanisms for these younger patients. This study is being conducted by Dr. Robert MacWilliams. Novel therapies are also being investigated such as the use of immunotherapy in conjunction with stereotactic body radiation to treat locally advanced pancreatic cancer. Mayo Clinic is part of the Alliance for Clinical Trials in Oncology which consists of approximately 10,000 oncologist sponsored by the NCI. As part of these multi-center trials, Mayo is involved studies using Abraxane and gemcitabine in local pancreatic cancer, Nivolumab with Abraxane and carboplatin in advanced pancreatic cancer, and rucaparib in patients with pancreatic cancer and a known BRCA mutation among several others. We also participate with the RTOG to investigate the effects of high or standard intensity radiation therapy in combination with chemotherapy. This wide variety of studies increases the likelihood of referrals to our institution for this novel protocol. Based on our past recruitment, the Mayo Clinic Rochester treats about 80 patients a year with locally advanced pancreatic cancer every year for the last 5 years. We believe that it would be reasonable to anticipate that we could recruit at least 5 patients into this study each year.

b.INNOVATION

Key innovations in this proposal are:

1. Development of the minimally invasive technique of EUS-guided PDT to provide effective, minimally invasive ablation of solid tumors of the pancreas (Phase II clinical trial). For patients choosing additional conventional chemotherapy, this will also provide the opportunity to assess the safety of giving chemotherapy in much closer time relationship to PDT than previously.
2. Use of contrast-CT as a clinically implementable technique for optimizing the light dose to predict the extent of PDT necrosis and so match this to the extent of disease without causing any unacceptable damage to adjacent normal structures.
3. Assessment of pancreatic tissue immediately preceding photoradiation to assess for verteporphyrin concentrations and potential biomarkers for response.

b.1 EUS-guided PDT will enable effective ablation of solid tumors of the pancreas.

Based on our collaborators at the University College London's previous animal experimental work, and our pre-clinical and clinical trials of pancreatic PDT, a phase I study of verteporfin PDT in locally advanced unresectable PanCa (VERTPAC-01) was undertaken. In the initial dose escalation part of the study, patients were treated with verteporfin PDT to assess its general safety profile, to determine the optimum treatment parameters needed to achieve effective and safe necrosis of tumor, and to confirm safety of administration of subsequent conventional palliative chemotherapy. Inclusion criteria included a histopathological/cytological diagnosis of PanCa, unresectable, non-metastatic disease confirmed at multidisciplinary review and adequate biliary drainage (serum bilirubin < 2.5 x upper limit of normal). All patients received a dose of verteporfin 0.4 mg/kg bodyweight intravenously, followed by light activation 60 minutes later under subdued lighting conditions. Treatment was via a single 10 mm tip diffuser fiber which was placed under CT guidance by an experienced radiologist (Figure 1). With increasing light doses, there was an increase in the extent of tumor necrosis around the fiber with no serious adverse events or reports of photosensitivity. This study aims to replicate these findings using the minimally invasive approach of EUS. Initially, only a single position of the laser fiber will be used, but in later patients multiple fiber positions will be used to show that it is possible to treat the full volume of appropriate cancers with endoscopic placement of the treatment fiber in more than one site. This is essential to show that endoscopic fiber placement can cover a comparable volume of tumor to the multi-fiber, percutaneous approach used in the previous studies.

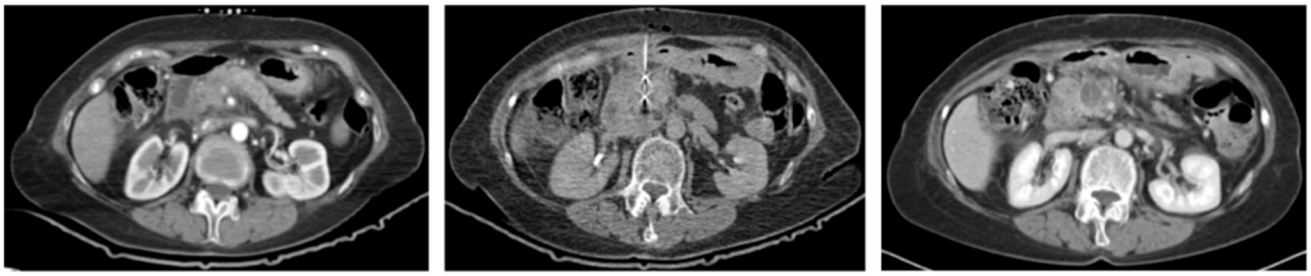

Fig. 2. Patient undergoing verteporfin PDT. The image on the left shows a baseline contrast-enhanced CT with a low attenuation mass in the head of the pancreas. The centre image shows percutaneous needle placement into the tumour. The image on the right shows the day 5 post PDT contrast-enhanced CT with a 2.67 cm^3 zone of necrosis in the region of the pancreatic head.

b.2: Use of contrast-CT to predict PDT response.

As reported in Project 4 and Core C, retrospective analysis of our Vertpac data showed that the CT venous phase contrast enhancement (when compared with CT without contrast), a measure of the blood concentration around the target zone, was strongly correlated with the volume of necrosis per unit of light energy deposited. This indicates that CT contrast should be a useful dose planning guide in future trials with photodynamic therapy.

c. APPROACH

c.1 (Aim 1) Phase II study of EUS-guided verteporfin PDT in solid pancreatic tumors (VERTPAC-c

c.1.a Objectives

Primary: To show that EUS-guided PDT to the pancreas is effective at direct ablation of advanced or locally advanced and small volume metastatic pancreatic tumors ***in a multicenter setting.***
Secondary: To evaluate the predictability of tumor necrosis as a function of delivered energy, based on pre-PDT contrast CT scans.
Tertiary: Evaluate the safety of chemotherapy given two days after PDT
Quarternary: Demonstrate that cancer biomarkers in pre- vs. post-PDT are surrogate markers of response.

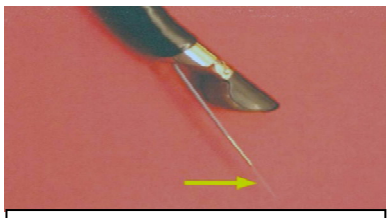

Fig. 4. Linear echoendoscope with optical diffuser fibre (arrow) extending from a 19G FNA needle.

c.1.b Design of *VERTPAC-02* study

This will be a phase II study of 15 (UCL) + 15 (Mayo) patients with histologically proven advanced or locally advanced PanCa or other solid tumors unsuitable for surgical resection. In the first 5+5 patients, EUS guided verteporfin PDT will be used with light delivered at just one site. In the following 10+10 patients, light will be delivered with the fiber at multiple positions, as required to ensure treatment of all appropriate areas of the cancer, as was done in the previous studies with percutaneous fiber insertion. Each patient will be given verteporfin 0.4 mg/kg bodyweight intravenously, followed by light activation 60 minutes after photosensitization (acceptable treatment window 60- 90 minutes). Light delivery will take place via a 5-20 mm length diffuser fiber placed under EUS guidance using red laser light at 690nm. The light dose delivered down the fiber will be fixed at 40 -80 J/cm, which was found to be optimum in our previous VERTPAC-01 study. All patients will be prescribed ciprofloxacin as a prophylactic to reduce the potential risk of infection associated with the fine needle puncture of the tumor. If a patient is allergic to ciprofloxacin, another acceptable broad spectrum antibiotic will be prescribed at the investigators discretion.

Patients will be evaluated by contrast enhanced CT at 2 days after PDT (treatment day 3), and they will be able to commence conventional palliative chemotherapy after that if they so wish within a week of PDT. Patients will also have additional blood draws taken for biomarker analysis before, during, and after their treatment. In previous studies, it was a protocol requirement that chemotherapy

not be given within a month of PDT. However, PDT is a local, one off treatment and chemotherapy is systemic and ongoing. It is an important innovation to give chemotherapy much earlier after PDT as our previous study on PDT for biliary tract cancer showed that delay in giving chemotherapy after PDT put patients at a disadvantage. Treatment response and time to disease progression will be assessed by CT scans at three-monthly intervals, as part of usual practice. Thereafter, patients will continue to be followed up for survival data. Second line chemotherapy and/or re-treatment with verteporfin PDT for progressive disease will be at the discretion of the investigators.

c.1.c Patient eligibility: See Table 1.

Inclusion Criteria	Exclusion Criteria
Histological/cytological Dx of advanced or locally advanced or small volume metastatic PanCa or other solid pancreatic tumor that is not amenable to curative surgical resection, or the patient is unfit, or declines surgery	For locally advanced patients, evidence of metastases other than lung or liver. For lung metastases, greater than three lesions and any lesions greater than 5cm are excluded. For advanced patients, any metastasis is acceptable for enrollment
Age > 18 years	Age < 18 yr; Porphyria; pregnant or breast-feeding
Measurable disease as defined by the Response Evaluation Criteria in Solid Tumors (RECIST)	Locally advanced disease involving > 50% circumference of the duodenum or a major artery within the treatment area
ECOG performance status 0, 1 or 2	ECOG performance status 3 or 4
Estimated life expectancy of at least 12 weeks	Previous treatment with curative intent for current disease within the past two weeks (i.e. prior resection, radical radiotherapy or chemotherapy)
Capable of giving written informed consent	Any psychiatric disorder making reliable informed consent impossible
Adequate biliary drainage (serum bilirubin < 2.5 ULN), with no evidence of active uncontrolled infection (patients on antibiotics are eligible)	A history of documented hemorrhagic diathesis or coagulopathy on therapeutic anticoagulation; History of prior or concomitant other malignancy that will interfere with the response evaluation
Women of child-bearing potential with a negative pregnancy test (qualitative serum HCG) prior to study entry AND must be using an adequate contraception method, which must be continued for 1 week after PDT	Any evidence of sever or uncontrolled systemic diseases or laboratory finding that in the view of the investigator makes it undesirable for the patient to participate in the trial
	Contrast allergy not amenable to treatment with steroids and antihistamines

Sample Size and Power Calculation

We have previously shown that the above treatment parameters result in at least a 12 mm region of necrosis around percutaneously placed fibers in PanCa, which will be considered criteria for a positive response. If we observe 16 (out of 30) patients with a positive necrosis region response around at least one of the fibers inserted, this would indicate that the true response rate is at least 53% (with 90% power and assuming a 25% variance), which will be significantly higher than the known response rate of at most 30% for palliative chemotherapy (50).

c.1.d Pre and post procedure assessments: See Table 2.

TABLE 2. Pre- and Post-Procedure Assessments for the VERTPAC-02 Study

Timepoint	Assessment
Pre-procedure	• Informed consent • Symptom and adverse event monitoring • Physical examination (including weight and ECOG performance status) • FBC, INR and biochemical profile including tumor markers (CEA/CA19-9), amylase, glucose • Pancreatic protocol CT chest, abdomen & pelvis (day -28 to 0) • Copy of report of prior histological or cytological proof of PanCa • QOL forms (EORTC QLQ30)
Post procedure	• Following treatment, patients will be monitored closely on the ward. The following protocol will be used to assess patients post treatment
Day 2 and 3 after the treatment on Day 1	• Symptom and adverse event monitoring, physical examination (including ECOG performance status) • FBC and biochemical profile including amylase, glucose • Pancreatic protocol CT on day 3, prior to planned discharge
Day 14	• Symptom and adverse event monitoring, physical examination (including ECOG status) • FBC and biochemical profile including amylase, glucose • QOL forms (EORTC QLQ30)
Months 3, 6 and 12:	• Symptom and adverse event monitoring; physical examination (including weight and ECOG status) • FBC and biochemical profile including CEA/CA19-9 • Pancreatic protocol CT

Clinical and laboratory assessments will be repeated prior to discharge (anticipated at day 3). All patients will be followed up on day 14 then at three, six and 12 months. At each visit, clinical symptoms will be reviewed, and quality of life and laboratory assessments repeated. In patients in good general condition with evidence of residual tumor or local tumor progression on repeat CT, up to two further PDT treatments may be offered at a minimum of four week intervals. If patients are unable to return for follow up they will be contacted by phone to complete the QOL assessment, as well as asked if they have had adverse events, hospitalization related to disease or progression of disease.

Criteria for early termination of the trial

As in our previous trials in this application, a DSMB will monitor toxicity. A grade 3 or 4 toxicity rate of >30% would be considered unacceptable. Therefore, if ≥13 patients (out of 25) suffer a grade 3/4 toxic event, the DMEC would consider stopping the trial because the likelihood of this occurring by chance alone is 0.02 (statistically significant at the 5% level) if the true toxicity rate were ≤30%.

c.1.e Photosensitizer protocol

After diagnosis and entry criteria are confirmed, patients will receive intravenous verteporfin 0.4 mg/kg bodyweight, 60 minutes before laser activation. The drug-light interval will be recorded to the nearest minute in the case report forms, with an acceptable treatment window being 60-90 minutes. This allows for the re-positioning of the fiber if multiple sites are to be treated. Patients will remain in subdued lighting on the ward for 24 hours after injection, followed by re-adaptation to indirect sunlight for increasing periods during the morning and late afternoon of the next day. Bright indoor light will be permitted after 24 hours and exposure to direct sunlight allowed after 48 hours.

c.1.f EUS-guided PDT Light Treatment

All laser procedures will be carried out in accordance with the local laser safety rules as specified by the hospital laser protection advisor. When the EUS needle has been confirmed to be correctly sited in the tumor under real-time EUS control, a diffuser fiber of appropriate length will be passed down to the tip of

the needle. Prior to use, the system will be calibrated to deliver 150 mW/cm along the length of each diffuser fiber, with the light dose delivered kept constant at 40 -80 J/cm. The illumination time is expected to be approximately 5 minutes based upon the linear irradiance and the target dose. After delivery of the planned light dose at each site, the needle and fiber will be removed.

c.1.g Dosimetry Studies: PS fluorescence and CT Perfusion

Two levels of dosimetry will be completed in this patient group. Initially we will complete PS dosimetry by placement of a bare tip fiber down the EUS guided needle, immediately prior to the treatment fiber placement. Fluorescence measurements will be completed with the Dartmouth Dosimeter system, measurements being taken at several points across the lesion. Data from the phase 1 trial was inconclusive about the value of this approach, because of high variability in placement, through the percutaneous needles used. The EUS needle placement is likely to be more convenient for sampling at more sites and to assess repeatability of multiple placements of the fiber, although patients will only have one EUS examination when they are photosensitised. We will also study the correlation between the PS fluorescence level seen and the perfusion (as measured by CT contrast) observed at the fiber location.

In the phase 1 trial, a strong correlation was seen between the volume of necrosis normalized by the light dose delivered, and CT contrast enhancement seen. We need to confirm this observation in the phase 2 trial when all subjects are receiving the same light dose. Thus, pre-treatment CT scans ± contrast will be acquired and used for all subjects recruited into this trial. Following analysis of these data, if the strong correlation is confirmed, we will then be able to recommend adjusting light delivery to modulate the anticipated volume of necrosis in future patient studies. Additionally, Project 4 is analysing this in the rabbit pancreas tumor model.

c.1.h Treatment Evaluation

PRIMARY Response evaluation

- Contrast-enhanced CT scans of the pancreas will be evaluated before treatment and on day 3 (after treatment on day 1), for measurement of tumor volume using RECIST criteria and to assess the extent of tumor necrosis after treatment.

SECONDARY Response evaluation

- Progression-free survival will be determined at 6 months follow-up and beyond.
- CEA and/or CA19.9 4-weekly if elevated prior to therapy
- ECOG performance status and Brief Pain Inventory pain scores, prior to therapy and at follow-ups
- Comparison will be made between the documented extent of necrosis and both the measured photosensitizer concentration, as assessed by fluorescence, and the estimated necrosis volume based on CT with and without contrast.

c.1.i Monitoring of serum biomarker expression pre- and post- treatment

Using different proteomic technologies we have identified several novel serum biomarkers which in combination with CA19-9 improve classification and lead time for detecting PanCa (unpublished and O'Brien, manuscript submitted to Gut). This work has used samples from diagnosed PanCa cases and relevant controls (biliary obstruction, chronic pancreatitis) and those taken up to 6 years prior to diagnosis from women enrolled onto the world's largest ever RCT, the United Kingdom Collaborative Trial of Ovarian Cancer Screening. We have identified several late markers (CA125, LRG1, CEA, MUC5AC) that are able to detect cancer in CA19-9-negative cases with several others showing detectable changes at least 12 months prior to the diagnosis (TIE2, vWF, AGR2). Marker panels combining these analytes are currently being validated for early detection using independent samples sets and we will next test them as predictive markers. We will examine modulations of these biomarkers in patients' serum pre- and post-verteporfin PDT using established ELISA assays. Assays will be carried out on all patient samples prior to, immediately following (Day 2/3), 14 days and 3 months post-

therapy. These will be correlated to clinical response to define surrogate markers of outcome that can be translated to future trials if effective in predicting response. Samples will also be retained for future studies aimed at proteomics-based discovery work in which we have considerable expertise (51). During the placement of the fibers, suction will be applied and an aspirate will be collected to examine the tissue present for verteporphyrin concentration and for the presence of fibroblast markers of activation (alpha-Smooth Muscle Actin, vimentin) to determine if this has an effect on PDT response.

6. PROTECTION OF HUMAN SUBJECTS

6.1. Risks to the subjects

6.1.1. Human Subjects Involvement and Characteristics

Patient Data Registration and Collection

If confirmed as eligible for a particular trial, the patient will be allocated a unique trial number and the treatment regimen defined. All study data will be recorded on case report forms at University College Hospital and Mayo Clinic. All research staff who enter data onto the case report form will have signed the study signature and delegation of duties log before undertaking data entry.

A password-protected, computer-based electronic database record of the study will be kept to facilitate statistical analysis. The study will be registered with the UCL data protection officer and comply with the Data Protection Act 1988. In addition, the study will be approved by the Mayo Clinic IRB and all records held in compliance with HIPPA requirements. Trial notes and source documents may be reviewed by the sponsor as part of internal audit or inspected by the regulatory authorities.

Subject selection

If confirmed as eligible, the patient will be consented and allocated a unique trial number and the treatment regimen defined. Ethnicity data will be collected. All study data will be recorded on case report forms. All research staff who enter data onto the CRF will have signed the study signature and delegation of duties log before undertaking data entry.

Withdrawal of Patients

When consenting to a particular trial, patients are consenting to trial treatment, trial follow-up and data collection. If a patient is withdrawn from trial treatment, follow-up and data collection will continue as per protocol. If the patient explicitly states their wish not to contribute further data to the study, the trial center should be informed in writing (letter or e-mail). Patients may be withdrawn from treatment for the following reasons:

Patient withdraws consent

Any change in the patient's condition which justifies the discontinuation of treatment in the clinician's opinion, e.g., progression, toxicity or intercurrent illness

Laser safety

The laser to be used will be a Opad L 690 nm, 0.3W Diode Laser or an OEM laser of similar specifications with 1% power stability . As this laser was not designed for clinical use the following extra safety measures will be adhered to above those required for routine clinical use: 1) As the laser can emit light even when no fiber is attached, a sign will be placed onto the machine warning operators to never look into the aperture, 2) A stop watch will be used to time the duration of light delivery, 3) The power output will be calibrated using a power meter. The laser will be approved for electrical safety by the hospital engineering department. This is the same laser parameters previously used at the University College London for the initial studies.

Photosensitizer protocol

Verteporfin (benzoporphyrin derivative monoacid ring A, BPD-MA; Visudyne^{TM}) is licensed in the UK for treatment of age-related macular degeneration and will be purchased from Novartis Pharmaceuticals UK Ltd (Surrey, UK) as a lyophilized lipid-formulated powder and stored in the Pharmacy department at UCLH. Investigational medicinal product (IMP) dispensing will be the responsibility of the clinical trial pharmacist at UCLH and dispensing records will be maintained in pharmacy. In the United States, Visuadyne is available from Bausch and Lomb (Bridgewater, New Jersey) and will be stored in the Mayo Clinic Research Pharmacy at the Saint Marys Campus of the Mayo Hospital. Labeling of drug will be carried out by pharmacy and include the term 'for investigational use only'. The lyophilized lipid-formulated powder will be mixed with distilled water to a final concentration of 2 mg/ml (previously referred to as liposomal formulation) by the chief investigator or appropriate members of his team. Investigational medical product (IMP) accountability will be the responsibility of the chief investigator. The dose, time of injection, lot

number and expiry date of the IMP will be recorded in the case report form.

Non-study Treatments

Patients may receive all concomitant therapy deemed to provide adequate supportive care at the investigator's discretion. All such medications or other treatments taken by the patient during the study (including those initiated prior to the start of the study) will be recorded in the patient's clinical notes and on the study case

report forms. No immunotherapy, hormonal therapy (excluding contraceptives and replacement steroids), or experimental medications will be permitted for three days post-phototherapy . Any disease progression requiring other forms of specific anti-tumor therapy will be a cause for early discontinuation in the study.

Discontinuation of therapy

A patient will discontinue a study under the following circumstances: (i) If the physician thinks it would be in the best interests of the patient, (ii) If the patient requests discontinuation, or (iii) If unacceptable toxicity is seen.

6.1.2. Sources of Materials

Data to be recorded from patient interviews and medical records will consist of historical data and laboratory values necessary for the care of the patient, that impact upon potential response to PDT therapy, including the patient's current and prior biopsy results (histological tumor type) and any laboratory values pertaining to the patient's overall health status.

Patient-specific Linkage/Subject I.D.: The patients' files will be coded by an ID number, maintained in a confidential location. Access to the data will only be possible by the Principal Investigator and by a small number of study personnel who will maintain confidentiality at all times.

6.1.3. Potential Risks

Risks and Guidelines for the Prevention of Toxicity

The major side effect of PDT is photosensitization. All patients who receive verteporfin will be photosensitive and will remain, for three to four days after injection, in subdued lighting. Bright indoor light will be permitted after the initial four day period, but patients must observe precautions to avoid exposure of the eyes and skin to direct sunlight for at least 3 days. Patients who receive verteporfin can be safely exposed to sunlight only two days after sensitization. The level of phototoxicity will vary for different areas of the body, depending on the extent of previous exposure to light. Before exposing any area of skin to direct sunlight or bright indoor light, the patient should test it for residual phototoxicity. A small area of skin should be exposed to sunlight for 10 minutes. If no phototoxicity reaction (erythema, edema, blistering) occurs within 24 hours, the patient can gradually resume normal outdoor activities, initially continuing to exercise caution and gradually allowing increased exposure. If a phototoxicity reaction occurs with the limited skin test, the patient should continue the existing precautions for another week before re-testing. As the tissue around the eyes may be more sensitive, it is not recommended that the face be used for testing. If a patient travels to a different geographical area with greater sunshine, they should retest their skin for phototoxicity. Ultraviolet (UV) sunscreens are of no value in protecting against phototoxicity reactions because photoactivation is caused by visible light. Ocular discomfort, commonly described as sensitivity to sun, bright lights, or car headlights, has also been reported in patients. For 30 days following treatment, patients should wear dark sunglasses when outdoors, and should consult their ophthalmologist if they notice any change in vision after treatment. All patients will be given information on barrier protection (hat, gloves, long sleeves etc) and an emergency
contact number will be given for patients and GPs. Similar precautions will be taken with verteporfin for a 48 hour period.

6.2. ADEQUACY OF PROTECTION AGAINST RISKS

6.2.1. Recruitment and Informed Consent

Written informed consent will be obtained from all patients according to the UCLH guidelines ‘Consent for research on human subjects’ or according to Human Subjects guidelines from the Mayo Clinic Institutional review board. The Investigator is required to explain the nature and purpose of the study to the patient prior to study entry. Consent to enter a particular trial must be sought from each patient or their legal representative only after a full explanation has been given, an information leaflet offered and time allowed for consideration. Signed patient consent should be obtained. The right of the patient to refuse to participate without giving reasons must be respected. When agreed by both parties, the patient will sign a consent form and be provided with a copy. One copy will be placed in the medical notes and the consent process documented. Consent will be obtained by the chief or one of the principal investigators. After the

patient has entered the trial the clinician will remain free to offer alternative treatment to that specified in the protocol at any stage, if he/she feels it is in the patient's best interest, but the reasons for doing. so should be recorded. In these cases the patients remain within the study for the purposes of follow-up and data analysis. All patients are free to withdraw at any time from the protocol treatment without giving reasons and without prejudicing further treatment.

6.2.2. Protection Against Risk

Adverse Events (Definitions)

An Adverse Event (AE) is defined as any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product regardless of the causal relationship with this treatment. Any adverse event or concurrent illness experienced by a patient during any portion of the study will be described in detail, fully evaluated and recorded on an adverse event form in the case report form by the investigator.

An *Unexpected Adverse Event* is defined as an adverse drug event the nature or incidence of which is not consistent with applicable product information.

A *Serious Adverse Event (SAE)* is defined as any untoward medical occurrence that at any drug dose results in:

- Death
- Inpatient hospitalization or prolongation of hospitalization
- A life-threatening event
- Severe or permanent disability
- Cancer (other than cancers diagnosed prior to enrolment in studies involving patients with cancer)
- Congenital anomaly

Note that as defined above, serious events, expected or not, are not necessarily causally associated with the study treatment. Those occurring during treatment and up to one month post-treatment will be reported promptly, and if assessed as a Suspected Unexpected Serious Adverse Reaction (SUSAR) within the timeframes (as specified in the Clinical Trials Regulations 2004) will be reported promptly to the appropriate authorities including the independent Data Monitoring and Ethics Committee (DMEC, see Section 5 below). The ultimate decision for the continuation of the trial lies with the DMEC.

All adverse effects will be assessed for the following:

- Severity (according to NCI toxicity criteria)
- Causality
- Expectedness (see below)
- Seriousness (see above)

Expected adverse events

- Related to the photosensitiser
- Photosensitivity
- Infusion related pain
- Vasovagal reaction
- Hypersensitivity reaction
- Related to percutaneously delivered photodynamic therapy
- Abdominal pain
- Nausea and vomiting
- Pancreatitis
- Bleeding
- Ileus
- Related to cancer progression
- Jaundice
- Anorexia and weight loss
- Cholangitis
- Duodenal obstruction
- Growth and metastasis of tumor

Pre-existing medical conditions

Any medical conditions present at baseline, which worsen after exposure to a study treatment, must be assessed and recorded as an AE on the adverse event form of the case report form.

Treatment-emergent adverse events

A treatment–emergent adverse event (TEAE) is defined as any event not present prior to exposure to study medication or any event that worsens in duration, intensity or frequency following exposure to study medication. The adverse event form of the case report form will be completed for all TEAEs.

Part of the adverse event documentation will involve the investigator making a drug related assessment. To promote consistency between investigators, the following elements should be taken into consideration along with good clinical judgment when determining the relationship of study medication to adverse event.

Existence of a temporal relationship between the event and the use of the study medication Ablation of the event when the study medication is withdrawn

Reappearance or worsening of the event when the study medication is re-administered

Previous experience with the study medication or related compounds

Influence of a pre-existing condition, concomitant disease or medication, or other environmental factors

The number of elements met and good clinical judgment should be used as a guide for determining the drug-related assessment. A binary assessment scale will be used to assess causality

Laboratory abnormalities

During the course of the study the investigator will be required to comment on any laboratory values outside the reference range. A laboratory abnormality will be regarded as an AE and recorded on the adverse event form of the case report form if according to the investigators judgment the value is significantly worse than at pre-treatment (significantly worse is defined by grade 3 or 4 by the NCI Toxicity criteria, version 3).

Assessment of trial safety

Annually the sponsor will provide the main REC and the MHRA with an annual safety report (ASR). The ASR will be prepared, using the sponsor's ASR form, by the Chief investigator or a delegated PI, reviewed by the sponsor and when necessary, be referred to an independent committee (independent to the trial) such as the safety committee. This will be done in accordance with the sponsor's SOP.

6.3. POTENTIAL BENEFITS OF THE PROPOSED RESEARCH TO THE SUBJECTS AND OTHERS

The patient will be counseled that he/she will not necessarily benefit directly from participation in this study. However, the possibility exists that such participation in the study will help to develop improved knowledge about the treatment of pancreatic cancer.

6.4. IMPORTANCE OF THE KNOWLEDGE TO BE GAINED

The human studies described in Aims 1 and 2 of this research project may provide knowledge and techniques that lead to a form of treatment that significantly improves the length and/or quality of life for patients with pancreatic carcinoma, who currently have a dismal prognosis.

6.5. DATA AND SAFETY MONITORING PLAN

Data Monitoring and Ethics Committee (equivalent to Data & Safety Monitoring Committee in US)

The role of the Data Monitoring and Ethics Committee (DMEC) or the Data and Safety Monitoring board (DSMB) is to provide independent oversight on the safety aspects of the trial. The DMEC will also determine the frequency and types of analyses. The committee will meet quarterly to review the data on safety and provide direction on whether a particular trial should continue or be stopped. Upon review of the data, the DMEC or DMSB committee has the power to recommend changes in the experimental protocol, which would additionally be reviewed, or to halt the trial pending further investigation of the data. Halting a trial will trigger an investigation by the Main REC and Sponsor, and the results of the investigation will be reported to the DMEC, TSC, the MHRA and the relevant pharmaceutical

company. A Data Safety Monitoring Committee will also be established at Mayo Clinic Rochester to monitor the study. Should an adverse event occur, it will be reported to both the DMEC and DSMB simultaneously. Should there be any disagreement on a course of action, the most conservative approach with the greatest safety for patients will be followed. (ie perform any recommended diagnostic studies and continue to observe the patient for the longest period recommended)

Trial Management Group

For each of the trials, a Trial Management Group led by the Chief Investigator (Dr Pereira) `will be responsible for overseeing the study. The Trial Management Group will agree protocol amendments prior to submission to Main REC and LREC. All investigators will be kept informed of important amendments.

Trial Center
The UCL/UCLH & RFH Joint Research Office (JRO) will be responsible for the day-to-day management of study D.1 and may also be approached to run the other studies. UCL will act as custodian of the data. The Trial Center will apply for Main REC approval. In addition, the Trial Center will ensure that all SAEs and SUSARs are appropriately reported to the relevant pharmaceutical company, Main REC and the MHRA, as well as to individual investigators. For Mayo Clinic patients, all serious complications or trial violations will be reported to the IRB of the Mayo Clinic as well as the RFH JRO.

Investigators Responsibilities
Individual investigators will have research ethics committee approval for all procedures upon initiation of each trial, and once approved they recruit patients, adhere to the most recent version of the protocol (taking into account any updated safety information and protocol amendments), conduct of the study, collect the data on the CRFs and prompt notification of adverse events. Investigators should refer SAEs as required by their research ethics committee. An agreement between the site and the Trial Center will be signed at the start of the trial.

Ethics Approval
The Trial Center will obtain approval from the Main UK Research Ethics Committee. The trial protocol must be submitted to each participating hospital's Local Research Ethics Committee (LREC). The Trial Center will require notification of favorable Site Specific Assessment before accepting patients into the trial. In addition, the Mayo Clinic IRB will approve this study.

Governance
Each study will be conducted in accordance with the recommendations for physicians involved in research on human subjects adopted by the 18th World Medical Assembly, Helsinki 1964 and later revisions, as well as the ICH Good Clinical Practice guidelines, the Medicines for Human Use (Clinical Trials) Regulations 2004 and the Research Governance Framework for Health and Social Care April 2005.

Regulatory issues
The trials will be reviewed by the Medicines and Healthcare products Regulatory Agency (MHRA) and authorization to conduct the trial will be received prior to commencement. Each trial will receive a Clinical Trials Authorization from the MHRA. The trials will be run to MRC/ICH Good Clinical Practice guidelines in accordance with the EU directive and in accordance with ICH GCP in non-EU countries. In the United States, approval will be sought from the institution IRB. All studies at the Mayo Clinic will be conducted in accordance with Good Clinical Practice Guidelines as well.

Audits & Inspection
The study may be subject to inspection and audit by the UCL/UCLH Joint Research Unit and other regulatory bodies, such as the MHRA, to ensure adherence to Medicines for Human Use (clinical trials) regulations 2004 (SI 2004/1031).

Sponsorship
Single center trials will be sponsored jointly by UCLH and UCL while multicenter trials will be sponsored by UCL. UCL will provide non negligent indemnity for the trial and negligent cover will be provided through the normal NHS mechanisms. UCLH/UCL will undertake adequate and appropriate monitoring of the trial to ensure compliance with applicable regulatory standards. The trial documentation and data may also be subject to internal auditing by UCLH/UCL.

6.1.6. ClinicalTrials.gov REGISTRATION REQUIREMENTS

Each of the studies (Aims 1, 2 and 3) will be registered at the ClinicalTrials.gov website, in the interest of sharing information with interested parties.

Inclusion of Women and Minorities

Women and minorities will be included in all trials, and entered into the trial based upon the population base at the institutions where the trial is being performed. Our estimates in the Targeted/Planned Enrollment Table are designed to reflect our local population base.
Children will not be included in this study as pancreatic cancer is extremely rare in children.

OMB Number: 0925-0002

Planned Enrollment Report

Study Title: Phase II study of EUS-guided verteporfin PDT in solid pancreatic tumors (VERTPAC-02)

Domestic/Foreign: Domestic

Comments: Additional recruitments only shown here in addition to the 25 at UCLH

Racial Categories	Ethnic Categories: Not Hispanic or Latino		Ethnic Categories: Hispanic or Latino		Total
	Female	Male	Female	Male	
American Indian/Alaska Native	0	0	0	0	**0**
Asian	0	0	0	0	**6**
Native Hawaiian or Other Pacific	0	0	0	0	**0**
Black or African American	1	1	0	0	**2**
White	14	14	0	0	**28**
More than One Race	0	0	0	0	**0**
Total	**15**	**15**	**0**	**0**	**30**

Study 2 of 3

Funding Opportunity Number: PAR-13-321. Received Date: 2014-02-10T11:49:46.000-05:00

Inclusion of Children

Cystic and solid tumors of the pancreas are overwhelmingly diseases of older adults, and our IRB applications for the studies will exclude individuals less than 18 years old. However, we would not want to preclude the participation of a young patient if they felt highly motivated and are able to give informed consent in the presence of a parent or guardian. In the unlikely event we have a person under the age of 18 eligible for one of the studies, we will write to the ethical committee requesting entry on compassionate grounds or exceptional circumstances.

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