SUPPLEMENTARY INFORMATION

METHODS

Trial governance and oversight

The sponsor was the University of Oxford and the study was coordinated by the Oncology Clinical Trials Office (OCTO) at the University of Oxford Clinical Trials Research Unit. A Trial Management Group was responsible for the day-to-day running of the study. A separate Safety Review Committee (SRC) was convened to review stage 1 data, decide on dose assignment and escalation, and conclude on the MTD of nelfinavir. Stage 2 data were reviewed by a Data Safety and Monitoring Committee. Broader trial supervision was provided by an independent Radiotherapy & Imaging Trial Oversight Committee.

Randomisation and masking

Patients in the open label stage 2 study component were randomised after three cycles of induction gem/nabP. Randomisation was carried out centrally in a 1:1:1:1:1 ratio using minimisation with a random element on a bespoke web-based system. The stratification factors were [WHO PS] and disease location, which was classified in error as [head/body] or [tail] rather than the planned [head] or [body/tail]. Post-randomisation, participants received one further cycle of gem/nabP before proceeding with standard-dose capecitabine-based CRT with nelfinavir (arm A) or alone (arm B), or high-dose CRT with nelfinavir (arm C) or alone (arm D). An initial 'calibration' arm E, in which participants were randomised to receive further three cycles of gem/nabP (no CRT), was later stopped when outcome in patients with LAPC receiving gem/nabP alone became available from the LAPACT trial[20]. No personnel were blinded to treatment assignment.

Treatments

All patients received four cycles of gem/nabP prior to CRT. Each 28 day cycle comprised of day 1, 8 and 15 intravenous infusions of nabP (125mg/m^2) followed immediately by gemcitabine (1000mg/m^2). Gemcitabine monotherapy was permitted for toxicities primarily resulting from nabP use. Twice daily oral capecitabine (830mg/m^2) was administered as concurrent therapy for CRT and taken on each day of radiotherapy. Following the outcome of the phase 1 dose finding study, nelfinavir was commenced at 1250mg twice daily seven days prior to the first fraction of CRT and continued until the day of the final fraction.

Radiotherapy planning and delivery

A detailed planning document was produced to guide radiotherapy provision and independently peer-reviewed by radiation oncologists who have a pancreatic cancer focus. An intravenous contrast-enhanced 3D or 4D CT was obtained in the treatment position for radiotherapy planning. For all patients in stage 1 and for standard dose CRT arms in Stage 2, 50.4Gy was delivered to the planning target volume (PTV) in five daily 1.8Gy fractions each week. High-dose CRT comprised of 54Gy delivered to an identically constructed PTV in 1.8Gy fractions, coupled with a simultaneous integrated boost to deliver a total of 60Gy in 2Gy fractions to a smaller volume encompassing the GTV with a small margin. There was no prophylactic nodal irradiation. Patients were treated in free breathing using mandated intensity modulated radiotherapy (IMRT) for high-dose treatment and either 3D conformal radiotherapy or preferably IMRT for standard dose radiotherapy.

Simulation and planning

A break in treatment of up to 28 days following induction systemic therapy was permitted prior to the start of CRT. Tumour volume was defined using all available imaging modalities, with a recommendation for support and joint contouring with a specialist radiologist. All radiotherapy was prescribed in accordance with ICRU 50/62 and delivered using photon beams of 6MV or higher energy. CRT commenced on a Monday or, where this was not possible, on a Tuesday.

Radiotherapy quality assurance

Radiotherapy quality assurance was coordinated by the National Radiotherapy Quality Assurance Group (RTTQA). The key principles were defined and updated as part of a specific *Radiotherapy Planning, Delivery and Quality Assurance Guidelines* document. This is available at http://www.rtttrialsqa.org.uk/rttqa/?q=scalop-2.

Radiotherapy dose constraints

Dose constraints are as provided in the **Appendix – protocol**. The dose to 95% of the PTV was required to be 93% or above with a maximum dose to a 0.1cc of 107% of the prescribed dose.

Management of unscheduled breaks

Unscheduled gaps were managed in line with guidance from the Royal College of Radiologists, entitled 'Timely delivery of radical radiotherapy: guidelines for the management of unscheduled treatment interruptions'.

Assessments

Patients were reviewed within seven days prior to day 1 of each cycle of gem/nab-pac. At this and all subsequent study reviews patients were assessed, their WHO performance status documented and treatment-related toxicity recorded as per Common Terminology Criteria of Adverse Events (NCI CTCAE), version 4.03. Bloods were drawn within two working days of day 1 of each gem/nab-pac cycle to assess CA19-9, full blood count (FBC) and both liver and renal function. Repeat bloods were sent for FBC, renal function and liver function on day 7 or 8, and day 14 or 15 of each cycle.

In stages 1 and 2, treatment response was assessed in the third or fourth week of cycle 3 of gem/nab-pac using CT imaging of the thorax, abdomen and pelvis. Disease measurement was undertaken as per RECIST v1.1. Briefly, radiologists were requested to define measurable, non-measurable, target and non-target lesions in line with RECIST 1.1 (www.recist.com). Measurable lesions must not have previously been irradiated and were required to be measurable via CT or MRI with a size at baseline of at least 10mm. Non-measurable lesions were all other lesions, including measurable but small lesions, previously irradiated lesions, brain metastases and skin lesions assessed by clinical examination. A maximum of five measurable lesions, with no more than two lesions per organ, were selected as target lesions representative of all lesions at baseline. All other lesions were regarded as non-target lesions. CT was the preferred modality of assessment and each identified and recorded lesion was re-characterized at each follow-up scan. As per RECIST, complete response was regarded as disappearance of all target lesions since baseline, partial response as a greater than 30% decrease in the sum of diameters of target lesions, stable disease as neither a 30% decrease nor a 20% increase in target lesion size and progressive disease at least a 20% increase in the sum of diameters of target lesions.

Patients randomized to arms A and C of stage 2, or who were in stage 1, were required to attend an additional review during the seven day pre-CRT nelfinavir induction week. Patients were reviewed weekly during CRT with bloods drawn for FBC, renal function and liver function on any day of each week of treatment. Additional blood was drawn for blood glucose measurement during week 1 of CRT. Dose limiting toxicities (DLTs) were assessed during each week of CRT and in the week following its completion for patients in stage 1. Patients in stage 2 were asked to complete HRQoL questionnaires during week 1 of CRT and in the week following treatment completion. Additional clinical reviews were conducted one week (and additional visit at three weeks for high-dose arm) following CRT completion

for stages 1 and 2, incorporating toxicity evaluation and blood samples for assessment of FBC, liver function and renal function. Patients were additionally asked to maintain a Diary and Accountability Log throughout treatment to track their compliance with capecitabine and, where applicable, nelfinavir.

The QLQ-C30, PAN26 and EQ5D health-related quality of life (HRQoL) questionnaires were completed once informed consent was gained but prior to the first cycle of chemotherapy for participants in stage 2 but not stage 1[21-23]. Regular assessments of WHO PS and treatment-related toxicity (as per NCI Common Terminology Criteria of Adverse Events (NCI CTCAE) version 4.03) were made throughout gem/nabP and CRT, as were measurements of full blood count, liver and renal function.

Patients were routinely reassessed at six, 18 and 28 weeks after CRT completion. At each of these timepoints, treatment response was evaluated by CT imaging of the thorax, abdomen and pelvis; a formal multidisciplinary team discussion of which was mandated to assess for resectability. Repeat HRQoL and toxicity assessments were also undertaken, as well as measurement of blood carbohydrate antigen (CA) 19-9, full blood count, liver function and renal function tests. Patients who progressed during treatment, or who were not randomized, constituted an observational cohort and data relating to date and site of any progression, subsequent treatments, date and cause of death and toxicity collected.

Statistical analysis

PFS and OS from date of registration were analysed using Cox proportional hazard (PH) models adjusting for randomised RT assignment (60Gy in 30# vs 50.4Gy in 28#), randomised nelfinavir assignment (+nelfinavir vs -nelfinavir) and minimisation factors (WHO performance status (0 vs 1) and disease location (head or body/tail). Events for PFS were progression according to response seen on cross sectional imaging (RECIST was used when possible). Where imaging was not possible, for example due to rapid deterioration in community, clinical suggestion of progression or CA19-9 rise or death without any known prior progression were considered as PFS events. Deaths by any cause was considered to calculate OS. Event-free patients were censored at the date last seen. Hazards ratios are presented with 60% CIs and one-sided p-values. The proportional hazards assumption was tested by use of Schoenfeld's global test, Cox-Snell residuals and visual plots. Median survival times with 60% CIs were obtained from the Kaplan-Meier product-limit estimate of the survivor function. Unadjusted p-values were derived from a log-rank test. For the two primary outcomes, possible interactions due to the factorial nature of the trial were assessed using Cox PH models that (1) included an interaction term between nelfinavir and RT assignment and (2) included all 4 randomised CRT arms. One-year OS

rates were estimated from Kaplan-Meier survivor functions at 12 months and between- arm % differences and CIs were estimated using the standard errors for the Kaplan-Meier survivor functions. Pearson's Chi-squared test was used to compare the number of patients with grade 3-4 AEs after CRT treatment and the numbers undergoing resection after randomisation. All survival outcomes were reported with 60% CIs since the primary analysis was powered with a one-sided alpha (type 1 error rate) of 20% such that the null hypothesis was H_0: HR≥1 and the alternative hypothesis was H_1: HR<1 (in favour of the dose-escalated radiotherapy arm for OS and in favour of nelfinavir for PFS).

HRQoL measures included the global health status (GHS) scale on the EORTC QLQ-C30 V3.0, 17 scales on the EORTIC-PAN26 V1.0, and the index score on the EQ-5D-5L. For each QoL outcome, scores at the end of CRT and at 6, 18, and 28 weeks post-CRT treatment were modelled using mixed linear model adjusting for time point, the pre- CRT outcome score, randomised RT assignment, nelfinavir assignment, minimisation factors, and a treatment group*timepoint interaction.

The median change and 95% CIs in CA19-9 values between 6 weeks post-CRT and pre-CRT were calculated using the binomial method using the centile command in STATA. All other secondary outcomes were descriptive: numbers (with %s) and medians [LQ,UQ] or means (SD) are presented. Local progression events were defined as local progression with or without metastases, or death by any cause. Local control was defined as alive with no known local progression, with or without existing metastasis. Distant progression events were defined as metastases with or without local progression, or death by any cause.

RESULTS

Compliance & safety

Of the 106 patients randomised to arms A-E, 11 (10.4%) patients withdrew from the study before completing cycle four of gemcitabine/nabP; 4/106 (3.8%) due to patient decision, 6/106 (5.7%) due to disease progression and 2/106 (1.9%) who became resectable following induction chemotherapy and proceeded to resection. One (1.1%) of 91 patients randomised to arms A-D did not start CRT, which was due to disease progression following gemcitabine/nabP. Only 2/91 (2.2%) patients commenced but did not complete CRT, which was due to new suspected dementia and patient decision. Both were in the standard dose CRT arms (A, B), with one assigned to the nelfinavir arm (arm A). A summary of compliance with different CRT components is provided in **Table 2**. A slightly higher proportion of patients who started CRT received more than 80% of prescribed capecitabine in the 60.0Gy RT arm (34/39; 87.2%) compared to the 50.4Gy arm (32/40; 80.0%). Over 70% (23/32) of patients allocated

to nelfinavir who commenced CRT received at least 70% of the planned dose, with tolerance similar between standard (12/16; 75%) and high-dose (11/16; 68.8%) radiotherapy arms. Of the 14 patients who commenced treatment on arm E, one (7.1%) stopped treatment after cycle 5 and 2 (14.3%) started but did not complete cycle six.

A summary of the proportion of patients who received subsequent anti-cancer treatment is provided in **Supp. Table 5**, though relevant data were only available for 41-58% of patients. There is variation of between 63.6-81.8% between comparator groups.

Safety

A summary of stage 1 adverse events (AEs) is provided in **Supp. Table 6.** In stage 2, there was no difference following the start of CRT in the rate of patients experiencing grade 3/4 adverse events between standard (n=10/45; 22.2%) and high (n=8/46; 17.4%) dose arms (chi-squared p=0.56; **Supp. Table 7**), nor with (n=9/38; 23.7%) or without (n=8/38; 21.1%) nelfinavir (chi-squared p=0.78; **Supp. Tables 8,9**). There were no treatment-related deaths.

A summary of adverse events reported prior to CRT is provided in **Supp. Table 10**. The most frequently reported grade 3/4 adverse events were pyrexia (n=16/91, 17.6%) and biliary sepsis (n=4/91, 4.4%), as well as vomiting, sepsis, neutropenic sepsis and cellulitis, which were each experienced by three (3.3%) of 91 participants. Cholangitis (n=2/91; 2.2%) was the most frequently reported grade 3/4 adverse event during CRT (**Table 3**), with no other grade 3/4 events reported in more than one patient. There were no treatment-related grade 5 events.

Quality of life measures

There was evidence for a difference between treatment arms in the severity of some symptoms when assessed by the PAN26 scale (**Figs. 3 & 4, Supp. Tables 21 & 22**). Reflecting a trend across studied timepoints, the adjusted mean difference (AMD) in pancreatic pain score was higher at 28 weeks post-CRT for high versus standard dose CRT (21.59, 95%CI 7.69-35.49). Similarly, altered bowel habit was higher for high dose CRT at 6- (AMD 13.77, 95%CI 2.1-25.45) and 18- (AMD 16.99, 95%CI 1.58-32.4) weeks post-CRT. At 6- weeks post-CRT, body image (AMD -13.17, 95%CI -25.8- -.54) and weight loss (AMD -14.49, 95%CI -27.61—1.37) favoured high-dose CRT, as did the 18-week sexuality score (-29.11, 95%CI -52.69- -5.53). Treatment burden was greater with nelfinavir treatment at the end of CRT (AMD 19.27; 95%CI 4.11-34.43) and 6-weeks post CRT (AMD 20.15; 95%CI 5.45-34.86). A large AMD in taste

change was also reported with nelfinavir at the end of CRT (27.2; 95%CI 10.29-44.1), and for dry mouth (AMD 17.26, 95%CI 1.39-33.12) at 18-weeks post-CRT, but this difference resolved at subsequent timepoints.