Site	Address	Principal investigator(s)
Recruitment to stages 1 &2		
Addenbrooke's	Cambridge University Hospitals NHS Foundation Trust, Hills Road, Cambridge, Cambridgeshire, CB2 0QQ	T Ajithkumar
Bristol Haematology & Oncology Centre	University Hospitals Bristol & Weston NHS Foundation Trust, Horfield Road Bristol, BS28ED	S Falk
Castle Hill Cancer Centre	Queen's Centre for Oncology & Haematology, Hull University Teaching Hospitals NHS Trust, Castle Road, Cottingham, HU16 5JQ	R Roy
Churchill Hospital	Oxford University Hospitals NHS Foundation Trust, Old Road, Headington, Oxford, Oxfordshire, OX3 7LE	S Mukherjee
Royal Free Hospital	Royal Free London NHS Foundation Trust, Pond Street, London, NW3 2QG	R Gilmore
Royal Surrey County Hospital	Royal Surrey NHS Foundation Trust, Egerton Road, Guildford, Surrey, GU2 7XX	S Cummins
Leeds Cancer Centre	St James's University Hospital, The Leeds Teaching Hospitals NHS Trust, Leeds, West Yorkshire, LS9 7TF	G Radhakrishna/R Goody
University Hospitals Coventry & Warwickshire	University Hospitals Coventry & Warwickshire NHS Trust, Clifford Bridge Road, Coventry CV2 2DX	M Scott-Brown
Velindre Cancer Centre	Velindre University NHS Trust, Velindre Road, Whitchurch, Cardiff, CF14 2TL	S Arif
Recruitment to stage 2 only		
Aberdeen Royal Infirmary	NHS Grampian, Foresterhill Road, Aberdeen, AB25 2ZN	A Shaukat, K Connolly
Belfast City Hospital	Belfast Health & Social Care Trust, Lisburn Road, Belfast, BT12 6BA	C Harrison
Nottingham City Hospital	Nottingham University Hospitals NHS Trust, Hucknall Road, Nottingham, NG5 1PB	L Aznar
Clatterbridge Cancer Centre	The Clatterbridge Cancer Centre NHS Foundation Trust, Clatterbridge Road, Bebington, Wirral, CH63 4JY	R Sripadam
Colchester Hospital	East Suffolk and North Essex NHS Foundation Trust, Turner Road, Colchester, CO4 5JL	SLoo

Derriford Hospital	University Hospitals Plymouth NHS Trust, Derriford Road, Crownhill, Plymouth, Devon, PL6 8DH	D Sherriff
Hammersmith Hospital	Imperial College Healthcare NHS Trust, Du Cane Road, London, W12 0HS	H Wasan
Milton Keynes University Hospital	Milton Keynes University Hospital NHS Foundation Trust, Standing Way, Eaglestone, Milton Keynes, MK6 5LD	W Saka
Norfolk & Norwich University Hospital	Norfolk & Norwich University Hospitals NHS Foundation Trust, Colney Lane, Norwich, NR4 7UY	D Holyoake
North Middlesex Hospital	North Middlesex University Hospital NHS Trust, Sterling Way, London, N18 1QX	L Melcher
The Christie Hospital	The Christie NHS Foundation Trust, Wilmslow Road, Manchester, M20 4BX	G Radhakrishna
University College Hospital Macmillan Cancer Centre	University College London Hospitals NHS Foundation Trust, London, WC1E 6AG	J Bridgewater
Weston Park Cancer Centre	Sheffield Teaching Hospitals NHS Foundation Trust, Witham Road, Sheffield, S10 2SJ	J Wadsley
Lincoln Oncology Centre	United Lincolnshire Hospitals NHS Trust, Lincoln, Lincolnshire, LN2 5QY	Z Stokes

Supplementary table 1: A list of centres that recruited to stages 1 and 2 of the SCALOP-2 trial. All centres are secondary or tertiary cancer centres that form part of the National Health Service in the United Kingdom. Principal Investigators based at each respective site are shown, as is whether they participated in stages 1 and 2 or only stage 2.

PRIOR TO RANDOMISATION TIMEPOINT	
Before starting induction treatment	**9 (5.7%)**
Treatment not started – reason not provided	5
Disease related adverse event	1
Investigator decision	1
Death	1
Identification of metastatic node outside of treatment field	1
After starting induction treatment but prior to the randomisation timepoint	**24 (15.1%)**
Toxicity	7
Disease progression	3
Investigator decision	3
Patient decision	3
Disease related adverse event	2
Death	2
Patient fitness	2
Tumour operable	1
Non-measurable disease	1
AT RANDOMISATION TIMEPOINT	
Ineligible for randomisation	**19 (11.9%)**
Progressive disease according to RECIST criteria	9
Tumour not encompassable by a radically treatable radiotherapy volume	5
WHO performance status >1	5
Loss of weight greater than 10% of baseline	5
Inadequate liver function test result	2
Inadequate renal function result	1

Supplementary table 2: A summary of reasons for withdrawal from stage 2 prior to randomisation.

Each reason for withdrawal is listed below the relevant timepoint at which withdrawal from the study occurred.

Baseline Factor		Dose Group[1]			Total (n=27)[1]
		1000 mg (n=11)	1250 mg (n=7)	Not Assigned (n=9)	
Age at registration (years) (n=11, 7, 9)		71.9 (50.2, 77.0)	67.3 (55.3, 74.7)	67.4 (49.3, 82.4)	69.2 (49.3, 82.4)
Time from pancreatic cancer diagnosis to registration (months) (n=11, 7, 9)		0.8 (0.2, 2.1)	1.2 (0.5, 2.3)	1.8 (1.1, 3.4)	1.2 (0.2, 3.4)
Gender	Male	27% (3)	43% (3)	22% (2)	30% (8)
	Female	73% (8)	57% (4)	78% (7)	70% (19)
Method of diagnosis of pancreatic cancer	Histologically	55% (6)	29% (2)	44% (4)	44% (12)
	Cytologically	27% (3)	71% (5)	56% (5)	48% (13)
	Both	18% (2)	0	0	7% (2)
Site of tumour within the pancreas	Head	64% (7)	86% (6)	89% (8)	78% (21)
	Body or tail	36% (4)	14% (1)	11% (1)	22% (6)
WHO performance status	0	45% (5)	43% (3)	67% (6)	52% (14)
	1	55% (6)	57% (4)	33% (3)	48% (13)
Any significant past/current medical conditions or surgical procedures (non-pancreatic cancer)?	Yes	91% (10)	100% (7)	100% (9)	96% (26)
	No	9% (1)	0	0	4% (1)
Any kidney disease?	Yes	0	0	0	0
	No	100% (11)	100% (7)	100% (9)	100% (27)
Any previous palliative bypass procedure or CBD stent?	Yes	27% (3)	29% (2)	44% (4)	33% (9)
	No	73% (8)	71% (5)	56% (5)	67% (18)
Any previous non-pancreatic cancer radiotherapy to upper abdomen?	Yes	0	0	0	0
	No	100% (11)	100% (7)	100% (9)	100% (27)
Height (cm) (n=11, 7, 9)		162.5 (150.0, 182.5)	169.0 (157.3, 173.0)	167.9 (154.0, 185.0)	166.0 (150.0, 185.0)
Weight (kg) (n=11, 7, 9)		76.3 (53.0, 89.9)	64.6 (49.7, 76.7)	70.0 (45.6, 110.6)	70.0 (45.6, 110.6)
Body surface area (m^2) (n=11, 7, 9)		1.8 (1.6, 2.1)	1.7 (1.5, 1.9)	1.8 (1.5, 2.1)	1.8 (1.5, 2.1)
Systolic blood pressure (mmHg) (n=9, 7, 8)		137.0 (116.0, 166.0)	143.0 (113.0, 177.0)	132.5 (106.0, 175.0)	138.5 (106.0, 177.0)
Diastolic blood pressure (mmHg) (n=9, 7, 8)		80.0 (63.0, 89.0)	79.0 (63.0, 91.0)	80.0 (70.0, 92.0)	79.5 (63.0, 92.0)
Pulse (beats/min) (n=9, 7, 8)		80.0 (69.0, 102.0)	86.0 (77.0, 98.0)	82.0 (75.0, 94.0)	84.5 (69.0, 102.0)
Temperature (°C) (n=9, 7, 8)		36.5 (36.1, 37.2)	36.7 (36.2, 37.0)	36.5 (35.9, 37.0)	36.6 (35.9, 37.2)
T Stage	T0/TX	0	0	0	0
	T1	0	0	11% (1)	4% (1)
	T2	18% (2)	0	11% (1)	11% (3)
	T3	18% (2)	29% (2)	11% (1)	19% (5)
	T4	64% (7)	71% (5)	67% (6)	67% (18)
N Stage	N0/NX	55% (6)	57% (4)	56% (5)	56% (15)
	N1	45% (5)	43% (3)	44% (4)	44% (12)
	N2	0	0	0	0
	N4	0	0	0	0
M Stage	M0	100% (11)	100% (7)	100% (9)	100% (27)
	M1	0	0	0	0

Supplementary table 3: Baseline patient and tumour characteristics for patients enrolled in stage 1 of the SCALOP-2 trial. [1]% (n) for categorical variables (percentage calculated using the total number in the respective group); median (min-max) for continuous variables

	Arm A (n= 19)	Arm B (n= 26)	Arm C (n= 19)	Arm D (n= 27)	A-D combined (n= 91)	Arm E (n= 15)	Observation cohort + early withdrawals (n= 53)	All registered (n= 159)
Longest diameter of primary lesion (mm)	0	1	0	0	1	0	1	2
CA19-9 concentration at C1D1 (U/mL)	1	2	0	3	6	1	10	17
Number of days from registration to start of induction chemotherapy	0	0	0	0	0	0	9	9
Longest diameter of primary lesion at randomisation (cm)	3	7	1	2	13	1	.	.
CA19-9 concentration at C3D1 (U/mL)	3	5	1	5	14	0	.	.

Supplementary table 4: A summary of missing data items for each of the stage 2 trial arms. Of the fourteen patients for whom there was missing data for largest diameter of primary lesion, four did not have a recorded measurement available and for the remainder the diameter was not measurable.

	Arm A (n=19)	**Arm B (n=26)**	**Arm C (n=19)**	**Arm D (n=27)**	**Arm E (n=15)**	**Obs cohort (n=53)**	**Total (n=159)**
Patients with data n (%)	11 (57.9)	14 (53.8)	11 (57.9)	11 (40.7)	10 (66.7)	22 (41.5)	79 (49.7)
Received subsequent treatment n (% out of patients with data)	9 (81.8)	10 (71.4)	7 (63.6)	9 (81.8)	10 (100)	20 (90.9)	65 (82.3)
Median time to first subsequent treatment for those who received treatment in months (LQ, UQ)[1]	3.4 (3.1, 5.0)	3.8 (3.3, 6.0)	5.1 (4.2, 7.5)	4.3 (3.6, 6.4)	4.1 (1.8, 8.3)	1.3 (0.7, 2.3)	3.6 (1.6, 5.3)

Supplementary table 5: A summary of subsequent treatment by stage 2 study arm. [1]The median time is out of patients who received subsequent treatment (second row), it is descriptive i.e. not Kaplan-Meier

AE Category n (%)	1000mg Dose Group (n=11)		1250mg Dose Group (n=7)	
	Grade 1-4	Grade 3-4	Grade 1-4	Grade 3-4
Blood & Lymphatic System Disorders	2 (18%)		3 (43%)	1 (14%)
Cardiac Disorders	1 (9%)	1 (9%)		
Ear and labyrinth disorders	1 (9%)			
Eye disorders	1 (9%)			
Gastrointestinal Disorders	9 (82%)	1 (9%)	5 (71%)	
General Disorders & Administration Site Conditions	7 (64%)	2 (18%)	1 (14%)	
Infections & Infestations	4 (36%)	2 (18%)	1 (14%)	1 (14%)
Injury; poisoning and procedural complications	2 (18%)		1 (14%)	
Investigations	4 (36%)	3 (27%)	3 (43%)	1 (14%)
Metabolism & Nutrition Disorders	4 (36%)	1 (9%)	2 (29%)	
Musculoskeletal & Connective Tissue Disorders	3 (27%)	1 (9%)		
Nervous System Disorders	2 (18%)			
Psychiatric disorders	3 (27%)		1 (14%)	
Reproductive system and breast disorders	2 (18%)			
Respiratory, thoracic and mediastinal disorders	2 (18%)		1 (14%)	
Skin and subcutaneous tissue disorders	3 (27%)		1 (14%)	
Vascular disorders	1 (9%)			

Supplementary table 6: A summary of adverse events reported during stage 1 of the trial, by nelfinavir dose. Percentages are shown as a proportion of the total number of patients in each dose group.

		50.4 Gy in 28# (n= 45)	60 Gy in 30# (n= 46)	Total (n= 91)
Before CRT				
Total no. of patients with grade 1-5 AEs		45 (100)	46 (100)	91 (100)
Patients with grade 3-4 AEs		27 (60)	35 (76.1)	62 (68.1)
	Grade 3-4 SAEs	13 (28.9)	24 (52.2)	37 (40.7)
	Grade 3-4 SARs/SUSARs	8 (17.8)	16 (34.8)	24 (26.4)
After the start of CRT		*(40 started CRT)*	*(39 started CRT)*	*(79 started CRT)*
Total no. of patients with grade 1-5 AEs		36 (80)	31 (67.4)	67 (73.6)
Patients with grade 3-4 AEs		10 (22.2)	8 (17.4)	18 (19.8)
	Grade 3-4 SAEs	8 (17.8)	6 (13)	14 (15.4)
	Grade 3-4 SARs/SUSARs	5 (11.1)	4 (8.7)	9 (9.9)
Chi-squared p-value*		0.56		

Supplementary table 7: A summary of the overall, and grade 3/4, adverse event, serious adverse event (SAE), serious adverse reaction (SAR) and suspected unexpected serious adverse reaction (SUSAR) rate prior to and following the start of chemoradiotherapy, by radiation dose. Adverse event rate includes SAEs, SARs and SUSARs which are then listed separately below. *Tests the null hypothesis that there is no difference in the number of post-CRT grade 3-4 adverse events between arms.

	CRT without nelfinavir (n= 38)	CRT with nelfinavir (n= 38)	Total (n= 76)
Before CRT			
Total no. of patients with grade 1-5 AEs	38 (100)	38 (100)	76 (100)
Patients with grade 3-4 AEs	25 (65.8)	30 (78.9)	55 (72.4)
Grade 3-4 SAEs	15 (39.5)	19 (50)	34 (44.7)
Grade 3-4 SARs/SUSARs	10 (26.3)	13 (34.2)	23 (30.3)
After the start of CRT	*(35 started CRT)*	*(32 started CRT)*	*(67 started CRT)*
Total no. of patients with grade 1-5 AEs	29 (76.3)	27 (71.1)	56 (73.7)
Patients with grade 3-4 AEs	8 (21.1)	9 (23.7)	17 (22.4)
Grade 3-4 SAEs	6 (15.8)	8 (21.1)	14 (18.4)
Grade 3-4 SARs/SUSARs	4 (10.5)	5 (13.2)	9 (11.8)
Chi-squared p-value*	0.78		

Supplementary table 8: A summary of the overall, and grade 3/4, adverse event, serious adverse event (SAE), serious adverse reaction (SAR) and suspected unexpected serious adverse reaction (SUSAR) rate prior to and following the start of chemoradiotherapy, with and without nelfinavir. Adverse event rate includes SAEs, SARs and SUSARs which are then listed separately below. *Tests the null hypothesis that there is no difference in the number of post-CRT grade 3-4 adverse events between arms.

	Arms A (50.4 Gy in 28# with nelfinavir) (n= 19)	Arms C (60 Gy in 30# with nelfinavir) (n= 19)	Total (n= 38)
Before CRT			
Total no. of patients with grade 1-5 AEs	3 (15.8)	3 (15.8)	6 (15.8)
Patients with grade 3-4 AEs	0 (0)	0 (0)	0 (0)
Grade 3-4 SAEs	0 (0)	0 (0)	0 (0)
After the start of CRT	*(16 started CRT)*	*(16 started CRT)*	*(32 started CRT)*
Total no. of patients with grade 1-5 AEs	8 (42.1)	9 (47.4)	17 (44.7)
Patients with grade 3-4 AEs	1 (5.3)	3 (15.8)	4 (10.5)
Grade 3-4 SAEs	0 (0)	1 (5.3)	1 (2.6)

Supplementary table 9: Rate of adverse events & serious adverse events (SAEs) attributed to nelfinavir. Adverse event count includes SAEs, which are then listed separately below.

		50.4 Gy in 28# (n= 45)		60 Gy in 30# (n= 46)		Total (n = 91)	
	Grade:	**1-5**	**3-4**	**1-5**	**3-4**	**1-5**	**3-4**
Haematological							
	Anaemia	1 (2.2)	0 (0)	1 (2.2)	1 (2.2)	2 (2.2)	1 (1.1)
	Neutropenia	0 (0)	0 (0)	2 (4.3)	2 (4.3)	2 (2.2)	2 (2.2)
	Febrile neutropenia	0 (0)	0 (0)	1 (2.2)	1 (2.2)	1 (1.1)	1 (1.1)
Gastrointestinal							
	Diarrhoea	2 (4.4)	0 (0)	5 (10.9)	3 (6.5)	7 (7.7)	3 (3.3)
	Vomiting	2 (4.4)	1 (2.2)	1 (2.2)	1 (2.2)	3 (3.3)	2 (2.2)
	Colitis	0 (0)	0 (0)	1 (2.2)	1 (2.2)	1 (1.1)	1 (1.1)
	Duodenal obstruction	0 (0)	0 (0)	1 (2.2)	1 (2.2)	1 (1.1)	1 (1.1)
	Nausea	0 (0)	0 (0)	1 (2.2)	0 (0)	1 (1.1)	0 (0)
	Dysphagia	0 (0)	0 (0)	1 (2.2)	1 (2.2)	1 (1.1)	1 (1.1)
General							
	Pyrexia	7 (15.6)	0 (0)	9 (19.6)	3 (6.5)	16 (17.6)	3 (3.3)
	Malaise	0 (0)	0 (0)	1 (2.2)	1 (2.2)	1 (1.1)	1 (1.1)
	Device occlusion	1 (2.2)	1 (2.2)	0 (0)	0 (0)	1 (1.1)	1 (1.1)
	Peripheral oedema	0 (0)	0 (0)	1 (2.2)	1 (2.2)	1 (1.1)	1 (1.1)
Hepatobiliary							
	Cholecystitis	1 (2.2)	1 (2.2)	1 (2.2)	1 (2.2)	2 (2.2)	2 (2.2)
	Jaundice cholestatic	0 (0)	0 (0)	1 (2.2)	1 (2.2)	1 (1.1)	1 (1.1)
Infections							
	Biliary sepsis	1 (2.2)	1 (2.2)	3 (6.5)	3 (6.5)	4 (4.4)	4 (4.4)
	Sepsis	1 (2.2)	1 (2.2)	2 (4.3)	1 (2.2)	3 (3.3)	2 (2.2)
	Cellulitis	0 (0)	0 (0)	3 (6.5)	3 (6.5)	3 (3.3)	3 (3.3)
	Neutropenic sepsis	2 (4.4)	2 (4.4)	1 (2.2)	1 (2.2)	3 (3.3)	3 (3.3)
	Lower respiratory tract infection	1 (2.2)	1 (2.2)	1 (2.2)	1 (2.2)	2 (2.2)	2 (2.2)
	Infection	0 (0)	0 (0)	1 (2.2)	1 (2.2)	1 (1.1)	1 (1.1)
	Device related infection	0 (0)	0 (0)	1 (2.2)	1 (2.2)	1 (1.1)	1 (1.1)
	Pneumonia	1 (2.2)	1 (2.2)	0 (0)	0 (0)	1 (1.1)	1 (1.1)
	Urinary tract infection	0 (0)	0 (0)	1 (2.2)	1 (2.2)	1 (1.1)	1 (1.1)
	Liver abscess	0 (0)	0 (0)	1 (2.2)	1 (2.2)	1 (1.1)	1 (1.1)
	Gastroenteritis viral	1 (2.2)	0 (0)	0 (0)	0 (0)	1 (1.1)	0 (0)
	Pleural infection	1 (2.2)	0 (0)	0 (0)	0 (0)	1 (1.1)	0 (0)
	Biliary tract infection	1 (2.2)	1 (2.2)	0 (0)	0 (0)	1 (1.1)	1 (1.1)
	Stoma site infection	1 (2.2)	1 (2.2)	0 (0)	0 (0)	1 (1.1)	1 (1.1)
	Upper respiratory tract infection	1 (2.2)	1 (2.2)	0 (0)	0 (0)	1 (1.1)	1 (1.1)
	Lung infection	0 (0)	0 (0)	1 (2.2)	1 (2.2)	1 (1.1)	1 (1.1)
Respiratory							
	Pulmonary embolism	2 (4.4)	2 (4.4)	0 (0)	0 (0)	2 (2.2)	2 (2.2)
	Chronic obstructive pulmonary disease	1 (2.2)	1 (2.2)	0 (0)	0 (0)	1 (1.1)	1 (1.1)

Supplementary table 10: A summary of adverse events reported prior to the first fraction of chemoradiotherapy, subdivided by trial arms and grade of severity.

Randomised comparison **(n= no. randomised)** ***(n=no. randomised before arm A and C closure)***	**60.0Gy RT in 30# Arms C+D** **(n=46)** ***(n=38)***	**50.4Gy RT in 28# Arms A+B** **(n=45)** ***(n=38)***	**CRT +nelfinavir Arms A+C** **(n=38)** ***(n=38)***	**CRT -nelfinavir Arms B+D** **(n=53)** ***(n=38)***
	Overall survival		**Progression-free survival**	
Numbers included	34	35	23	34
No. events n (%)	24 (70.6)	22 (62.9)	21 (91.3)	28 (82.3)
Median survival (60% CI)	17.5 (16.4, 20.7)	20.8 (15.7, 26.8)	10.3 (10.0, 11.6)	11.8 (10.6, 15.7)
Adjusted HR (60% CI), one-sided p-value	1.31 (1.02, 1.70), p=0.81		1.63 (1.26, 2.11), p=0.95	

Supplementary table 11: Per-protocol analyses for overall survival by radiation dose and progression free survival by nelfinavir usage.

Randomised comparison **(n= no. randomised)** ***(n=no. randomised before arm A and C closure)***	**60.0Gy RT in 30#** **Arms C+D** **(n=46)** ***(n=38)***	**50.4Gy RT in 28#** **Arms A+B** **(n=45)** ***(n=38)***	**CRT +nelfinavir** **Arms A+C** **(n=38)** ***(n=38)***	**CRT -nelfinavir** **Arms B+D** **(n=53)** ***(n=38)***
	Overall survival		**Progression-free survival**	
Sensitivity analysis 1: test for RT dose and nelfinavir interaction				
Interaction term (80% CI), two-sided p-value	1.57 (0.80, 3.09), p=0.39		0.82 (0.42, 1.62), p=0.71	
Sensitivity analysis 2: multi-arm comparison				
Numbers included	Arm C: 19 Arm D: 19	Arm A: 19 Arm B: 19	Arm A: 19 Arm C: 19	Arm B: 19 Arm D: 19
No. events n (%)	Arm C: 16 (84.2) Arm D: 14 (73.7)	Arm A: 14 (73.7) Arm B: 14 (73.7)	Arm A: 16 (84.2) Arm C: 19 (100)	Arm B: 15 (78.9) Arm D: 17 (89.5)
Adjusted HR (60% CI)	D vs B 0.87 (0.62, 1.21)		A vs B 1.91 (1.37, 2.66)	

Supplementary table 12: Sensitivity analyses for overall survival by radiation dose and progression free survival by nelfinavir usage.

Events* within 12 months of registration n (%)	**60 Gy in 30#** **Arms C+D (n= 46)**	**50.4 Gy in 28#** **Arms A+B (n= 45)**	**CRT without nelfinavir** **Arms B+D (n= 38)**	**CRT with nelfinavir** **Arms A+C (n= 38)**
Local progression (with or without metastasis)	**11 (23.9)**	**15 (33.3)**	**11 (28.9)**	**12 (31.6)**
Metastasis (no local progression)	**16 (34.8)**	**11 (24.4)**	**9 (23.7)**	**15 (39.5)**
Deaths	**12 (26.1)**	**11 (24.4)**	**7 (18.4)**	**12 (31.6)**
Deaths after local progression (with or without metastasis)	**3 (6.5)**	**7 (15.6)**	**2 (5.3)**	**5 (13.2)**
Deaths after metastasis (no local progression)	**9 (19.6)**	**4 (8.9)**	**5 (13.2)**	**7 (18.4)**
Deaths before any known progression	**0**	**0**	**0**	**0**
No local progression and alive	**26 (56.5)**	**26 (57.8)**	**22 (57.9)**	**19 (50)**
followed up for <12 months (with metastasis)	**1 (2.2)**	**0**	**1 (2.6)**	**0**
followed up for <12 months (no known progression)	**1 (2.2)**	**1 (2.2)**	**0**	**0**
followed up for >12 months (with metastasis)	**6 (13.0)**	**7 (15.6)**	**3 (7.9)**	**8 (21.1)**
followed up for >12 months (no known progression)	**18 (39.1)**	**18 (40)**	**18 (47.4)**	**11 (28.9)**

Supplementary table 13: Data relating to local control at one year, by study arm. *Events refer to the first recorded event. Events where both local and distant progression were present at first diagnosis of progression are recorded as local progression (with or without metastasis).

	Arms E (n=15)
No. deaths n (%)	12 (80.0)
Median overall survival (60% CI)	21.3 (20.2, 23.4)
No. PFS events n (%)	15 (100)
Median progression free survival (60% CI)	12.4 (6.0, 14.4)
No. deaths within one year	3 (20)
One-year overall survival rate months 60% CI	80.0% (69.6, 87.2)
No. of patients with AEs n (%)	15 (100)
Patients with grade 3-4 AEs n (%)	13 (86.7)
No. of patients with SAEs n (%)	8 (53.3)
Patients with grade 3-4 SAEs n (%)	4 (26.7)
Patients undergoing resection post-randomisation n (%)	Yes: 2 (13.3) No: 13 (86.7) (Those with no data assumed no resection, 8 patients did not have any data)
No. of local progressions (with or without metastasis) n (%)	15 (100)
Disease response at **4** weeks post-treatment (complete response/partial response/stable disease/progressive disease)	Complete response: 0 Partial response: 2 Stable disease: 7 Progressive disease: 1 Not evaluable: 2 No scan data: 3

Supplementary table 14: Survival and disease control outcomes for stage 2 trial arm E.

	Observation cohort (n=53)
No. deaths n (%)	46 (86.8)
Median overall survival (60% CI)	9.3 (8.4, 9.6)
No. of PFS events n (%)	48 (90.6)
Median progression free survival (60% CI)	3.6 (2.8, 5.6)
No. deaths in one year	35 (66.0)
One-year overall survival rate months n (%)	30.1% (24.7, 35.6)

Supplementary table 15: Survival and disease control outcomes for the observation cohort.

	Questionnaires expected n	Questionnaires received n (% of patients alive)					
		QLQ C-30		PAN26		EQ-5D	
		Data available	Completed	Data available	Completed	Data available	Completed
Start of CRT	80	80 (100)	74 (92.5)	80 (100)	74 (92.5)	80 (100)	71 (88.8)
End of CRT	80	75 (93.8)	51 (63.8)	76 (95)	51 (63.8)	76 (95)	49 (61.3)
6 weeks post-CRT	80	75 (93.8)	55 (68.8)	75 (93.8)	56 (70)	75 (93.8)	55 (68.8)
18 weeks post-CRT	73	55 (75.3)	34 (46.6)	55 (75.3)	34 (46.6)	55 (75.3)	32 (43.8)
28 weeks post-CRT	61*	46 (75.4)	26 (42.6)	45 (73.8)	25 (41)	46 (75.4)	25 (41.0)

Supplementary table 16: Data availability for each of the three assessed health-related quality measures at each of the five assessed timepoints. *Sixty patients were alive to 28 calendar weeks after CRT but one additional patient took the questionnaire early, prior to death, and has been included.

Global Health status	**50.4 Gy in 28# (n= 45)**		**60 Gy in 30# (n= 46)**		**Total (n=91)**		**Adjusted* mean difference between arms (95% CI)**
	n	Median [LQ, UQ]	n	Median [LQ, UQ]	n	Median [LQ, UQ]	
Start of CRT	35	66.7 [33.3, 75]	38	66.7 [58.3, 83.3]	73	66.7 [50, 83.3]	-
End of CRT	28	66.7 [50, 83.3]	21	75 [58.3, 83.3]	49	66.7 [50, 83.3]	3.04 (-7.6, 13.67)
6 weeks post-CRT	25	75 [58.3, 83.3]	29	75 [58.3, 83.3]	54	75 [58.3, 83.3]	-4.98 (-14.87, 4.9)
18 weeks post-CRT	12	66.7 [54.2, 79.2]	21	66.7 [58.3, 75]	33	66.7 [58.3, 75]	-3.34 (-16.79, 10.1)
28 weeks post-CRT	11	66.7 [50, 83.3]	13	75 [50, 83.3]	24	70.8 [50, 83.3]	-0.18 (-15.08, 14.72)

Supplementary table 17: EORTC QLQ-C30 score by chemoradiotherapy dose. *Model adjusting for time point (end of CRT/6/18/28 weeks post-CRT), GHS score at the start of CRT, RT treatment group (arms A+B vs C+D), nelfinavir assignment (arms A+C or B+D), WHO PS (0 or 1), disease location (head or body/tail) and RT treatment group*timepoint interaction. Model included a random intercept for patient effect.

EQ5D index score	**50.4 Gy in 28# (n= 45)**		**60 Gy in 30# (n= 46)**		**Total (n=91)**		**Adjusted* mean difference between arms (95% CI)**
	n	Median [LQ, UQ]	n	Median [LQ, UQ]	n	Median [LQ, UQ]	
Start of CRT	35	.8 [.71, .88]	36	.81 [.73, .86]	71	.81 [.71, .88]	-
End of CRT	25	.75 [.66, .91]	23	.84 [.72, .88]	48	.8 [.68, .89]	.04 (-.11, .18)
6 weeks post-CRT	25	.75 [.66, .88]	29	.8 [.72, .91]	54	.79 [.72, .91]	.03 (-.11, .17)
18 weeks post-CRT	14	.75 [.63, .85]	25	.71 [.1, .75]	39	.71 [.58, .8]	-.15 (-.32, .02)
28 weeks post-CRT	20	.46 [0, .72]	23	.62 [0, .84]	43	.52 [0, .8]	-.08 (-.24, .08)

Supplementary table 18: EQ-5D-5L score by chemoradiotherapy (CRT) dose. *Model adjusting for time point (end of CRT/6/18/28 weeks post-CRT), GHS score at the start of CRT, RT treatment group (arms A+B vs C+D), nelfinavir assignment (arms A+C or B+D), WHO PS (0 or 1), disease location (head or body/tail) and RT treatment group*timepoint interaction. Model included a random intercept for patient effect.

Global Health status	**CRT without nelfinavir (n= 38)**		**CRT with nelfinavir (n= 38)**		**Total (n= 76)**		**Adjusted* mean difference between arms (95% CI)**
	Scores n	Median [LQ, UQ]	n	Median [LQ, UQ]	n	Median [LQ, UQ]	
Start of CRT	33	66.7 [50, 75]	30	66.7 [58.3, 83.3]	63	66.7 [50, 83.3]	-
End of CRT	21	66.7 [50, 83.3]	21	66.7 [58.3, 83.3]	42	66.7 [50, 83.3]	0.69 (-10.16, 11.53)
6 weeks post-CRT	25	75 [58.3, 83.3]	24	75 [58.3, 83.3]	49	75 [58.3, 83.3]	-4.37 (-14.31, 5.56)
18 weeks post-CRT	14	66.7 [58.3, 75]	14	66.7 [58.3, 75]	28	66.7 [58.3, 75]	-4.94 (-18.12, 8.23)
28 weeks post-CRT	11	75 [50, 83.3]	9	66.7 [50, 75]	20	66.7 [50, 83.3]	-6.47 (-21.84, 8.89)

Supplementary table 19: EORTC QLQ-C30 score by nelfinavir use. *Model adjusting for time point (end of CRT/6/18/28 weeks post-CRT), GHS score at the start of CRT, RT treatment group (arms A+B vs C+D), nelfinavir assignment (arms A+C or B+D), WHO PS (0 or 1), disease location (head or body/tail) and RT treatment group*timepoint interaction. Model included a random intercept for patient effect.

EQ5D index score	**CRT without nelfinavir (n= 38)**		**CRT with nelfinavir (n= 38)**		**Total (n=76)**		**Adjusted* mean difference between arms (95% CI)**
	Scores available n	Median [LQ, UQ]	Scores available n	Median [LQ, UQ]	Scores available n	Median [LQ, UQ]	
Start of CRT	31	.8 [.72, .88]	30	.8 [.67, .84]	61	.8 [.71, .88]	-
End of CRT	19	.8 [.57, .88]	23	.8 [.66, .91]	42	.8 [.66, .88]	.03 (-.13, .19)
6 weeks post-CRT	24	.74 [.63, .94]	25	.78 [.72, .85]	49	.78 [.66, .88]	.1 (-.05, .25)
18 weeks post-CRT	16	.71 [.34, .8]	18	.72 [.62, .8]	34	.71 [.58, .8]	.01 (-.16, .18)
28 weeks post-CRT	19	.62 [0, .77]	18	0 [0, .74]	37	.5 [0, .77]	-.13 (-.29, .04)

Supplementary table 20: EQ-5D-5L score by nelfinavir use. *Model adjusting for time point (end of CRT/6/18/28 weeks post-CRT), GHS score at the start of CRT, RT treatment group (arms A+B vs C+D), nelfinavir assignment (arms A+C or B+D), WHO PS (0 or 1), disease location (head or body/tail) and RT treatment group*timepoint interaction. Model included a random intercept for patient effect.

Scale	Pre- CRT score median [LQ,UQ]		Adjusted* mean difference between RT arms (95% CI)			
	50.4 Gy in 28# (n= 45)	60 Gy in 30# (n= 46)	End of CRT	6 weeks post-CRT	18 weeks post-CRT	28 weeks post-CRT
pancreatic pain	12.5 [8.3, 25]	8.3 [0, 25]	1.28 (-9.02, 11.58)	6.28 (-3.55, 16.1)	11.09 (-1.53, 23.72)	21.59 (7.69, 35.49)
eating related items	16.7 [0, 33.3]	16.7 [0, 33.3]	-1.91 (-14.9, 11.08)	-1.21 (-13.59, 11.17)	-5.99 (-21.93, 9.95)	4.95 (-12.62, 22.52)
Hepatic	0 [0, 8.3]	0 [0, 16.7]	-7.36 (-15.34, .61)	-1.04 (-8.62, 6.54)	6.32 (-3.73, 16.37)	-.21 (-11.26, 10.85)
altered bowel habit	33.3 [8.3, 41.7]	33.3 [16.7, 50]	3.04 (-9.26, 15.33)	13.77 (2.1, 25.45)	16.99 (1.58, 32.4)	12.52 (-4.33, 29.37)
body image	33.3 [16.7, 66.7]	33.3 [16.7, 66.7]	-5 (-18.19, 8.18)	-13.17 (-25.8, -.54)	-11.48 (-28.17, 5.22)	-8.33 (-26.47, 9.81)
health care satisfaction	100 [83.3, 100]	100 [83.3, 100]	-11.49 (-27.84, 4.87)	12.35 (-3.45, 28.14)	10.47 (-9.87, 30.81)	-5.08 (-27.48, 17.33)
Sexuality	33.3 [0, 100]	50 [0, 100]	7.08 (-11.52, 25.67)	-8.66 (-26.91, 9.59)	-29.11 (-52.69, -5.53)	-4.65 (-29.95, 20.66)
swollen abdomen	0 [0, 33.3]	0 [0, 33.3]	.51 (-12.88, 13.9)	.6 (-12.15, 13.36)	15.17 (-1.3, 31.63)	10.98 (-7.16, 29.12)
taste changes	33.3 [0, 33.3]	33.3 [0, 66.7]	-6.1 (-21.92, 9.71)	-9 (-24.01, 6)	-4.7 (-23.91, 14.51)	-4.24 (-25.41, 16.93)
Indigestion	0 [0, 33.3]	0 [0, 33.3]	-6.18 (-18.36, 6.01)	-4.43 (-15.93, 7.08)	-1.58 (-16.39, 13.24)	4.11 (-12.27, 20.49)
Flatulence	33.3 [0, 66.7]	33.3 [0, 66.7]	-2.12 (-17.21, 12.97)	4.77 (-9.43, 18.98)	12.11 (-6.77, 30.99)	-10.48 (-31.37, 10.41)
weight loss	0 [0, 33.3]	0 [0, 33.3]	-6.59 (-20.37, 7.19)	-14.49 (-27.61, -1.37)	-12.17 (-29.35, 5.02)	-12.03 (-30.91, 6.84)

Scale	Pre- CRT score median [LQ,UQ]		Adjusted* mean difference between RT arms (95% CI)			
	50.4 Gy in 28# (n= 45)	60 Gy in 30# (n= 46)	End of CRT	6 weeks post-CRT	18 weeks post-CRT	28 weeks post-CRT
loss of muscle strength	33.3 [16.7, 33.3]	33.3 [0, 66.7]	4.65 (-8.94, 18.23)	.11 (-12.96, 13.18)	-7.19 (-23.58, 9.2)	10.26 (-7.43, 27.94)
dry mouth	16.7 [0, 33.3]	33.3 [0, 33.3]	6.43 (-6.06, 18.92)	-6.96 (-19.02, 5.1)	-4.59 (-20.1, 10.92)	-4.62 (-21.5, 12.26)
burden of treatment	33.3 [33.3, 66.7]	33.3 [33.3, 33.3]	-12.77 (-26.33, .79)	5.99 (-7.48, 19.47)	-11.01 (-28.27, 6.26)	-10.6 (-29.13, 7.94)
fear of future health	33.3 [33.3, 66.7]	33.3 [33.3, 66.7]	-4.9 (-20.17, 10.38)	-10.35 (-25.24, 4.53)	-5.75 (-24.74, 13.25)	.57 (-20.36, 21.51)
ability to plan future	50 [33.3, 66.7]	33.3 [0, 66.7]	3.47 (-13.47, 20.41)	9.48 (-6.83, 25.79)	-.11 (-21.82, 21.61)	23.03 (-1.23, 47.28)

Supplementary table 21: Adjusted mean difference in EORTIC-PAN26 score immediately, 6-, 18- and 28- weeks following standard (50.4Gy in 28 fractions) and high (60Gy in 30 fractions) dose chemoradiotherapy. *Model adjusting for time point (end of CRT/6/18/28 weeks post-CRT), GHS score at the start of CRT, RT treatment group (arms A+B vs C+D), nelfinavir assignment (arms A+C or B+D), WHO PS (0 or 1), disease location (head or body/tail) and RT treatment group*timepoint interaction. Model included a random intercept for patient effect.

Scale	Pre- CRT score median [LQ,UQ]		Adjusted* mean difference between nelfinavir arms (95% CI)			
	CRT without nelfinavir (n= 38)	CRT with nelfinavir (n= 38)	End of CRT	6 weeks post-CRT	18 weeks post-CRT	28 weeks post-CRT
pancreatic pain	8.3 [0, 16.7]	8.3 [8.3, 33.3]	5.02 (-6.9, 16.94)	2.67 (-8.39, 13.73)	-1.98 (-15.85, 11.89)	2.97 (-13.22, 19.17)
eating related items	16.7 [0, 33.3]	16.7 [0, 33.3]	3.27 (-10.82, 17.37)	12.64 (-.56, 25.85)	-5.04 (-21.72, 11.64)	13.43 (-6.05, 32.91)
Hepatic	0 [0, 16.7]	0 [0, 16.7]	-3.5 (-12.38, 5.38)	7.36 (-.89, 15.62)	7.71 (-3.15, 18.57)	-4.76 (-17.35, 7.84)
altered bowel habit	33.3 [16.7, 50]	33.3 [0, 50]	2.72 (-10.3, 15.74)	-12.15 (-24.23, -.07)	-14.41 (-30.49, 1.66)	-12.33 (-30.95, 6.29)
body image	33.3 [16.7, 66.7]	33.3 [16.7, 66.7]	14.32 (.62, 28.01)	-.83 (-13.66, 12)	14.55 (-2.11, 31.22)	2.74 (-16.42, 21.9)
health care satisfaction	100 [83.3, 100]	100 [83.3, 100]	-8.9 (-26.39, 8.59)	-9.12 (-25.76, 7.52)	-20.27 (-41.73, 1.18)	-17.79 (-42.37, 6.79)
Sexuality	33.3 [0, 100]	33.3 [0, 100]	-11.16 (-30.9, 8.58)	-3.48 (-22.73, 15.76)	-9.08 (-33.69, 15.52)	2.78 (-23.91, 29.47)
swollen abdomen	0 [0, 33.3]	0 [0, 33.3]	8.6 (-5.09, 22.29)	3.41 (-9.29, 16.11)	4.72 (-11.64, 21.07)	1.33 (-17.88, 20.55)
taste changes	33.3 [0, 33.3]	33.3 [0, 66.7]	27.2 (10.29, 44.1)	11.27 (-4.51, 27.06)	-.53 (-20.34, 19.28)	5.56 (-17.54, 28.66)
Indigestion	0 [0, 33.3]	0 [0, 33.3]	1.38 (-11.67, 14.44)	3.91 (-8.27, 16.08)	14.99 (-.25, 30.23)	-8.1 (-25.95, 9.76)
Flatulence	33.3 [0, 66.7]	33.3 [0, 66.7]	-2.32 (-18.04, 13.4)	-8.72 (-23.31, 5.87)	.32 (-18.64, 19.28)	-16.13 (-38.38, 6.11)

Scale	Pre- CRT score median [LQ,UQ]		Adjusted* mean difference between nelfinavir arms (95% CI)			
	CRT without nelfinavir (n= 38)	CRT with nelfinavir (n= 38)	End of CRT	6 weeks post-CRT	18 weeks post-CRT	28 weeks post-CRT
weight loss	33.3 [0, 33.3]	0 [0, 33.3]	12.76 (-2.43, 27.95)	9.8 (-4.22, 23.83)	12.03 (-6.28, 30.34)	16.61 (-4.47, 37.69)
loss of muscle strength	33.3 [33.3, 66.7]	33.3 [33.3, 66.7]	8.46 (-6.21, 23.14)	10.71 (-3.16, 24.57)	8.97 (-8.36, 26.3)	.84 (-18.81, 20.5)
dry mouth	33.3 [0, 33.3]	33.3 [0, 33.3]	3.6 (-9.47, 16.68)	4.27 (-7.99, 16.54)	17.26 (1.39, 33.12)	1.36 (-16.98, 19.71)
burden of treatment	33.3 [33.3, 66.7]	33.3 [33.3, 66.7]	19.27 (4.11, 34.43)	20.15 (5.45, 34.86)	6.49 (-12.28, 25.26)	14.75 (-6.6, 36.1)
fear of future health	66.7 [33.3, 83.3]	33.3 [33.3, 66.7]	3.59 (-12.73, 19.9)	-3.59 (-19.28, 12.09)	-7.17 (-26.98, 12.64)	7.67 (-14.98, 30.32)
ability to plan future	33.3 [33.3, 66.7]	33.3 [0, 66.7]	13.43 (-3.62, 30.48)	4.83 (-11.22, 20.89)	-.06 (-21.37, 21.25)	2.92 (-21.86, 27.69)

Supplementary table 22: Adjusted mean difference in EORTIC-PAN26 score immediately, 6-, 18- and 28- weeks following chemoradiotherapy with and without concurrent nelfinavir. *Model adjusting for time point (end of CRT/6/18/28 weeks post-CRT), GHS score at the start of CRT, RT treatment group (arms A+B vs C+D), nelfinavir assignment (arms A+C or B+D), WHO PS (0 or 1), disease location (head or body/tail) and RT treatment group*timepoint interaction. Model included a random intercept for patient effect.