Name of Sponsor/Company: Cardiff University (SPON830-10)	Individual Study Table Referring to Part of the Dossier Volume: Page:	*(For National Authority Use only)*
Name of Finished Product: N/A		
Name of Active Ingredient: N/A		

Title of Study:

A Phase II study of neoadjuvant chemotherapy given before short course preoperative radiotherapy (SCPRT) as treatment for patients with MRI-staged operable rectal cancer at high risk of metastatic relapse

Investigators:

Dr Simon Gollins

Study centre(s):
Sites that recruited patients:

- Southampton General Hospital
- Charing Cross Hospital
- The Christie Hospital
- Clatterbridge Cancer Centre
- Huddersfield Royal Infirmary
- Glan Clwyd Hospital
- Ysbyty Gwynedd
- Wrexham Maelor Hospital
- Royal Preston Hospital
- Calderdale Royal Infirmary
- Blackpool Victoria Hospital
- York Hospital
- Bristol Haematology and Oncology Centre
- St James's University Hospital

Non recruiting sites:

- Cheltenham General Hospital
- St Mary's Hospital
- University Hospitals Coventry and Warwickshire
- Gloucestershire Royal Hospital
- Velindre Cancer Centre
- Royal Surrey Country Hospital

Publication (reference):

The main publication for the trial is currently being prepared, we expect to submit for publication in the third quarter 2017.

Studied period (years): (date of first enrolment) 15th May 2012 (date of last completed) 29th November 2015	Phase of development: Phase II

Objectives:

The overall aim of the current Phase II study is to develop a feasible, safe and active regimen incorporating 8 weeks of neoadjuvant chemotherapy prior to SCPRT then immediate surgery which can be taken forward into a large future Phase III trial to be tested against the current standard treatment of SCPRT alone followed by immediate surgery

The primary objective of this research is to ask:

In MRI-defined operable rectal cancer patients, is it feasible to introduce eight weeks of oxaliplatin/5-FU (OxMdG) chemotherapy prior to SCPRT then immediate surgery? Feasibility will be assessed as the percentage of patients undergoing surgery (primary end-point).

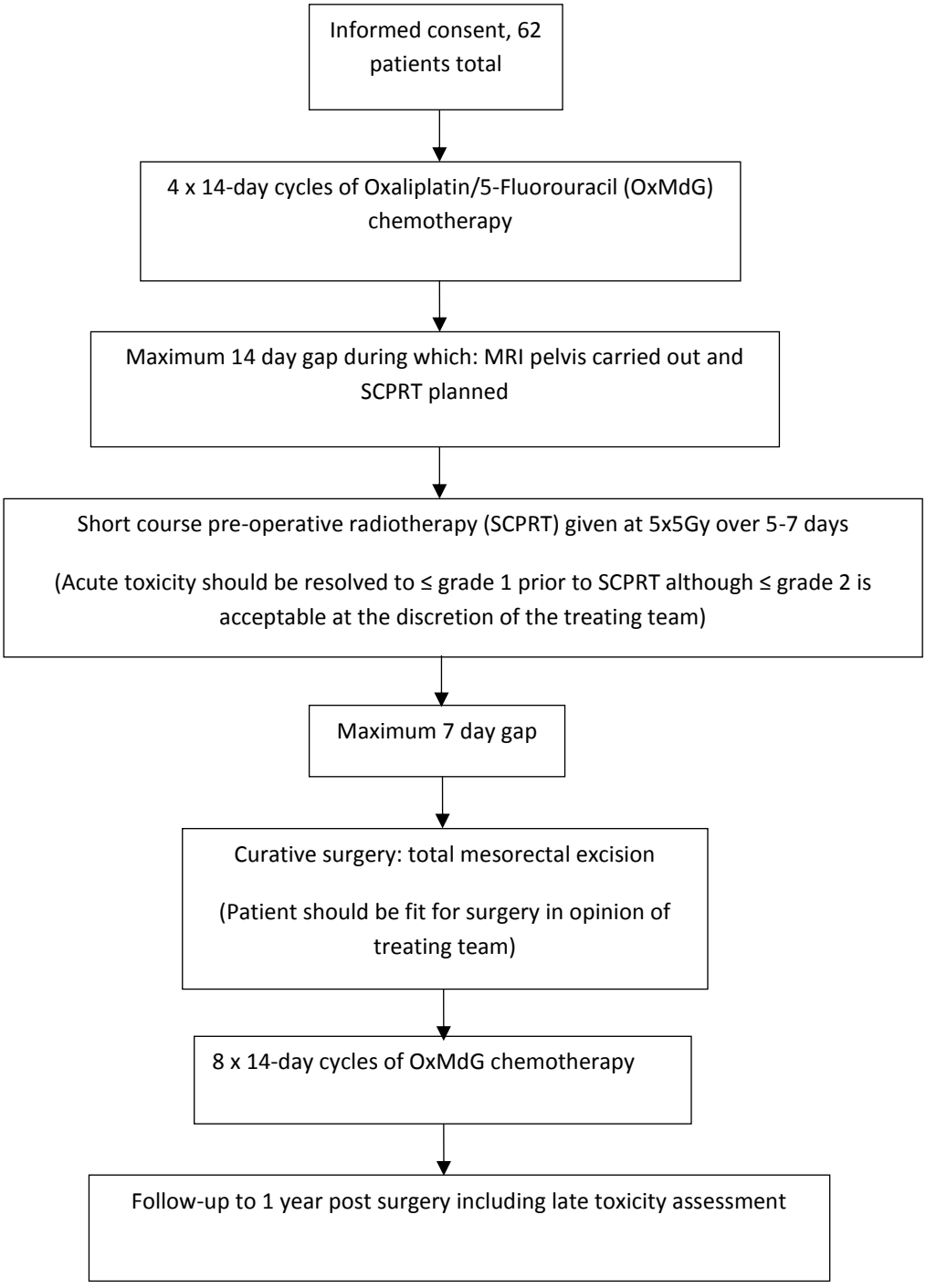
The secondary objectives of this research are to ask:

1. Is the treatment feasible? The additional assessments of achieved chemotherapy and radiotherapy dose intensity will be used in addition to eligible patient refusal rates to enter the trial.

2. Is such an approach safe? Safety will be measured using NCI Common Terminology Criteria for Adverse Events (CTCAE) v4.02 together with assessment of postoperative morbidity/mortality.

3. How active is the neoadjuvant chemotherapy element in terms of downstaging the rectal cancer? Histological measurements of response will be assessed in the resected surgical specimen including the percentage of patients exhibiting a pathological complete response (pCR), T and N stage compared to the pre-treatment MRI scan, tumour regression grade and tumour cell density measurement. A second MRI scan following neoadjuvant chemotherapy but before SCPRT will be also used to assess neoadjuvant chemotherapy downstaging efficacy in terms of T and N stage and tumour regression grade.

Methodology:



Number of patients (planned and analysed):
62 patients planned, 60 recruited.

Diagnosis and main criteria for inclusion:

Main inclusion criteria:

1. Patient 18 years old or older
2. Tumour biopsy with histopathological confirmation of rectal adenocarcinoma
3. Inferior aspect of tumour is not less than 4 cm from anal verge on digital examination and pelvic MRI scan
4. Superior aspect of tumour is not higher than the anterior aspect of the S1/S2 interspace on pelvic MRI scan
5. Further high-resolution MRI defined inclusion criteria include:
    - Mesorectal fascia is <u>not</u> threatened or involved (i.e. tumour is > 1mm from mesorectal fascia)
    - Primary tumour is:
        - T3a-b (mesorectal primary tumour invasion seen ≤ 5 mm beyond muscularis propria) in the presence of either:
            - extra-mural vascular invasion or
            - mesorectal lymph node(s)/tumour deposit(s) of any size with irregular border or mixed signal intensity
        - any T3c (primary tumour invasion seen >5mm beyond muscularis propria)-T4a (invasion of visceral peritoneum for tumours with a component above the peritoneal reflection)
    - Low tumours should not involve levator ani (i.e. there is >1 mm gap between tumour and levator ani) or anal sphincters
6. ECOG performance status 0-1

Main exclusion criteria:

1. Disease threatening mesorectal fascia (i.e. disease ≤ 1 mm from mesorectal fascia whether this is primary tumour, extra-mural vascular invasion or tumour deposit with irregular border and mixed signal intensity)
2. Stage T4b cancer with invasion into adjacent organs or structures
3. Enlarged pelvic sidewall (internal iliac) lymph nodes considered to be involved

Test product, dose and mode of administration, batch number:

The investigational medicinal products (IMPs) used in this trial are oxaliplatin and 5-fluorouracil (5-FU) with the option of replacing 5-FU with capecitabine during post-operative adjuvant chemotherapy.

Oxaliplatin and 5-FU are given as an intravenous infusion and are indicated for the treatment of colon cancer in an adjuvant setting. Oxaliplatin is an antineoplastic drug belonging to a new class of platinum based compounds which exhibits a wide spectrum of both *in vitro* cytotoxicity and *in vivo* anti-tumour activity. Oxaliplatin formulation: Hospira 5 mg/ml Concentrate for Solution for Infusion or Hospira 5 mg/ml Powder for Solution for Infusion.

5-FU is an analogue of uracil, a component of ribonucleic acid and is believed to function as an

antimetabolite. Capecitabine is an oral pro-drug that is enzymatically converted to 5-FU. 5-FU Fluorouracil formulation: 25 mg/ml Injection.

Capecitabine is indicated for the treatment of stage III colon cancer and metastatic colorectal cancer and is routinely used as a combination therapy with oxaliplatin in an adjuvant setting. Capecitabine Xeloda formulation: 150mg and 500mg Film-coated Tablets.

Oxaliplatin, 5-FU and capecitabine are sourced locally by the Trust Pharmacy. The trial does not mandate a specific drug (IMP) supplier.

Duration of treatment:

All patients will receive OxMdG neo-adjuvant chemotherapy (4 x 14-day cycles of IV OxMdG, oxaliplatin 85mg/m² plus levofolinic acid 175 mg, 5-Fluorouracil 400 mg/m² (bolus), then 5-Fluorouracil 2400 mg/m^2) followed by SCPRT (25Gy over 5 fractions) and surgery.

All patients will then receive 8 x 14-day cycles of post-operative adjuvant OxMdG chemotherapy as above. Patients unable to have 5-FU post operatively will receive capecitabine using a 2-weekly 9-days-on, 5-days-off schedule (1250mg/m^2 orally bi daily).

Reference therapy, dose and mode of administration, batch number:

N/A, single arm study

Criteria for evaluation:

Primary outcome measure

- Feasibility: The proportion of patients who commence neoadjuvant chemotherapy who then undergo surgical resection of their rectal cancer.

Secondary outcome measures

- Feasibility:
  - Achieved dose intensity for chemotherapy and radiotherapy
  - Patient recruitment in terms of refusal rates of eligible patients to enter the trial
- Safety:
  - NCI CTCAE version 4 toxicities including postoperative complication rate (up to 30 days postoperatively)
  - Late toxicity assessment at 1 year following surgery
- Activity:
  - Histological assessment of downstaging efficacy in the resected specimen including the percentage of patients exhibiting a pathological complete response (pCR), and tumour cell density measurement
  - Radiological assessment of downstaging efficacy comparing baseline MRI with 9-week post-chemotherapy MRI in terms of T and N stage and tumour regression grade
  - Local recurrence-free, distant metastasis-free, disease-free, and overall survival

Statistical methods:

It is felt that if more than 92% (as was found in CR07), and certainly not less than 80%, of patients complete protocol treatment up to and including surgery then it would warrant further investigation in the Phase III setting. Basing on a A'Hern design looking at proportion of patients completing protocol

treatment up to and including surgery and setting p0=0.80, p1=0.92, 90% power, alpha=0.1 would require 57 patients (50 successes).

Primary analysis will be the proportion of participants (with 80% confidence intervals) who complete surgery.

Secondary analysis will include the following analyses:

- Toxicity data will be summarised: SAEs will be listed and toxicities, postoperative complication rates, and late radiation toxicity will be presented in tabular format. Tolerability and feasibility of use will be summarised in terms of the number of treatment reductions, delays and treatment withdrawals.
- Proportion of eligible patients (identified on screening logs at sites) who gave consent to be enrolled into the trial
- The proportion of patients exhibiting a pathological complete response at surgery
- Radiological assessment of down-staging efficacy comparing baseline MRI with 9-week post-chemotherapy MRI
- OS will be calculated from the time of enrolment to date of event or date censored (date last known to be alive). OS will be presented as median time-to-event and with Kaplan-Meier curves. OS at 12 months following surgery will also be presented.
- The proportion of local recurrence-free, distant metastasis-free, and disease-free patients will be assessed at 12 months after surgery.

SUMMARY - CONCLUSIONS

60 patients were enrolled from 14 UK centres between 25 May 2012 and 11 June 2014 (Figure 1). At the time of analysis, all patients had completed at least one year of post-surgical follow up or withdrawn from the study. Patient and tumour baseline characteristics are shown in Table 1.

EFFICACY RESULTS:

Efficacy, pTRG, TCD, PFS

Table 1 shows the results from the 9 week MRI. T Stage was downstaged in 44/60 (73%), unchanged in 12/60 (20%), and missing for 4/60 (7%) of patients. N Stage was downstaged in 36/60 (60%), unchanged in 22/60 (37%), and missing for 2/60 (3%) of patients.

Data on the surgical procedure and pathology results are shown in Table 4. 7/57 (12%) patients were found to have had a complete regression (pTRG) and these were confirmed by a central review that included a check of the number of deeper levels cut on the entirely embedded scars. Univariate ordinal logistic regression showed no evidence of a relationship between pTRG and the number of baseline MRI risk factors (z=-0.06, p=0.951) or biopsy TCD (z=0.29, p=0.774, n=57), but strong relationships between pTRG and resection greatest TCD (z=-5.70, p<0.001, n=57), whole TCD (z=-5.41, p<0.001, n=57), and whole as % of biopsy TCD (z=-4.03, p<0.001, n=57).

The median follow up for PFS was 27.3 months (95% CIs: 24.5-30.1). Of the 60 patients enrolled in the trial, 10 had a progression (8 distant (6 lung, 1 liver, 1 small bowel), and 2 local recurrences) at the time of analysis. The PFS rate at 2 years was 86.2% (95% CIs: 74.3-92.9). One patient died after 2.3 years.

Univariate cox regression showed some evidence of a relationship between pTRG (when split by complete/good vs moderate/minimal/none) and progression free survival (PFS) (see Figure 3): HR=4.76 (95% CIs: 0.60-37.61, p=0.0712). When TCD was included as a continuous variable in a univariate cox regression, there was some evidence that larger resection greatest TCD was associated with worse PFS (HR 1.03, 95% CI: 1.00-1.07, p=0.066) but evidence for association with other TCDs was weak: biopsy TCD HR 1.01 (95% CI: 0.96-1.06, p=0.725), resection whole TCD HR 1.04 (95% CI: 0.99-1.10, p=0.137).

SAFETY RESULTS:

Toxicities during neoadjuvant (end of cycle 1 to post SCPRT assessment) and adjuvant (end of cycle 5 to end of cycle 12) treatment periods are shown in Table 2. The rate of any grade 3+ toxicity was the same in each treatment period: neoadjuvant 24/60 (40%) and adjuvant 15/45 (33%), with neutrophil count decrease being the most common toxicity in each case: 12/60 (20%) and 5/45 (11%) respectively. There were no deaths during treatment (including the post-surgical period). There was no evidence of a difference between baseline (median: 84.1kg, IQR: 78.1-92.1) and pre-surgical (median: 85.3kg, IQR: 76.1-92.7) weight (z=0.796, p=0.426, n=56). Post-surgical complications within 30 days are show in Table 3. Out of the 57 patients who had surgery, 49 (86%) were discharged within 30 days a median of 7 (IQR: 6-11) days after surgery.

Table 1. Baseline characteristics and 9 week MRI results

		Baseline	**9 weeks**
		n (%)*	**n (%)***
Patients enrolled	N	60	
Age (years)	Median (IQR,range,n)	63 (56.5-70,38-79,60)	
Sex	Male	44 (73.3)	
	Female	16 (26.7)	
ECOG performance status	0	55 (91.7)	
	1	5 (8.3)	
Predominant differentiation of primary tumour	Well	5 (8.3)	
	Moderate	49 (81.7)	
	Poor	2 (3.3)	
	Unknown	4 (6.7)	
Time from MRI scan to registration (weeks)	Median (IQR,range,n)	3.7 (2.6-4.6,0-5.9,60) prior to reg	9.4 (8.7-10,7.4-12.4,58) after reg
MRI - Craniocaudal length (mm)	Mean (SD,range,n)	49 (11.9,28-80,58)	34.3 (13.5,7-70,52)
MRI - Height from anal verge (mm)	Mean (SD,range,n)	79 (21.5,40-140,58)	82.9 (21.8,35-140,52)
MRI T Stage	T0		4 (7)
	T1		1 (2)
	T2	1 (1.7)	28 (47)
	T3a	17 (28.3)	6 (10)
	T3b	24 (40)	13 (22)
	T3c	14 (23.3)	4 (7)
	T3d	1 (1.7)	0 (0)
	T4a	3 (5)	0 (0)
	Missing	0 (0)	4 (7)

MRI N Stage	N0	7 (11.7)	38 (63)
	N1	39 (65)	18 (30)
	N2	14 (23.3)	2 (3)
	Missing	0 (0)	2 (3)
MRI M Stage	M0	60 (100)	58 (97)
	Missing	0 (0)	2 (3)
MRI - CRM involvement	Clear	59 (98.3)	57 (95)
	Missing data	1 (1.7)	2 (3)
MRI - Extramural vascular invasion	Positive	25 (41.7)	9 (15)
	Negative	35 (58.3)	49 (82)
	Missing	0 (0)	2 (3)
Number of baseline MRI risk factors out of T>=3c or N1-2 or EMVI+	3	11 (18.3)	
	2	14 (23.3)	
	1	35 (58.3)	

Table 2. CTCAE v4.02 grade 3+ toxicity in patients during neoadjuvant (week 1 to post SCPRT assessment) and adjuvant (post cycle 5 to post cycle 12 assessment) treatment

System organ class	**Adverse event**	**Neoadjuvant n (%)***	**Adjuvant n (%)****
Any	*Any*	*24 (40)*	*15 (33)*
Cardiac disorders	Pericarditis	1 (2)	0 (0)
Gastrointestinal	Abdominal pain	0 (0)	2 (4)
	Diarrhoea	1 (2)	3 (7)
	Dyspepsia	1 (2)	0 (0)
	Gastritis	1 (2)	0 (0)

	Nausea	1 (2)	1 (2)
	Rectal obstruction	0 (0)	1 (2)
	Stomatitis	2 (3)	0 (0)
General disorders and administration site conditions	Injection site reaction	0 (0)	1 (2)
	Localized oedema	1 (2)	0 (0)
Infections and infestations	Upper respiratory infection	1 (2)	2 (4)
Injury, poisoning and procedural complications	Vascular access complication	1 (2)	0 (0)
Investigations	Neutrophil count decreased	12 (20)	5 (11)
	Platelet count decreased	2 (3)	1 (2)
	Weight loss	0 (0)	1 (2)
	White blood cell decreased	1 (2)	1 (2)
Metabolism and nutrition disorders	Hyperuricemia	0 (0)	1 (2)
Nervous system disorders	Neuropathy	1 (2)	0 (0)
	Syncope	1 (2)	0 (0)
Psychiatric disorders	Agitation	1 (2)	0 (0)
	Anxiety	1 (2)	0 (0)
Respiratory, thoracic and mediastinal disorders	Cough	1 (2)	0 (0)
Skin and subcutaneous tissue disorders	Palmar-plantar erythrodysesthesia syndrome	0 (0)	1 (2)
	Rash	1 (2)	0 (0)
Vascular disorders	Thromboembolic event	2 (3)	0 (0)

Table 3. Post-surgery complications within 30 days of operation

		n (%)*
Anastomotic dehiscence	Yes	3 (5)
	No	50 (88)
	Unknown	4 (7)
Perineal wound dehiscence	Yes	3 (5)
	No	50 (88)
	Unknown	4 (7)
Pelvic infection/collection requiring draining	Yes	10 (18)
	No	43 (75)
	Unknown	4 (7)
Serious infection elsewhere	Yes	9 (16)
	No	44 (77)
	Unknown	4 (7)
Serious infection elsewhere - location	Wound	6 (67)
	Spleen	1 (11)
	Unknown	2 (22)
Venous thromboembolic event	Yes	0 (0)
	No	53 (93)
	Unknown	4 (7)
Death within 30 days	No	57 (100)
Myocardial infarction	Yes	0 (0)
	No	53 (93)
	Unknown	4 (7)
Cerebrovascular accident	Yes	0 (0)
	No	53 (93)
	Unknown	4 (7)

Other complications	Fast atrial fibrillation	1 (2)
	Post-operative ileus	1 (2)
	Ureteric Stenosis from pelvic collection	1 (2)
	Fluid discharge and foecal matter passing PR grade 1	1 (2)
	Diarrhoea grade 3	1 (2)
	Abdominal ascites grade 3	1 (2)
Second operation required	Yes	4 (7)
	No	49 (86)
	Unknown	4 (7)
If yes, what was done?	Laparotomy and Hartmann's	1 (2)
	Laparotomy, Resection of loop jejunostomy & re-formation of end illostomy	1 (2)
	Ureteric Stent	1 (2)
	Rectal suture repair of anastomosis ileus 1 week post-op	1 (2)
Time spent on ITU/HDU post op (days)	0	31 (54)
	1 to 3	17 (30)
	5 to 7	4 (7)
	16	1 (2)
	Unknown	4 (7)
Was patient discharged within 30 days?	Yes	49 (86)
	No	4 (7)
	Unknown	4 (7)
If discharged within 30 days, time from surgery to discharge (days)	Median (IQR,range,n)	7 (6-11,2-23,49)
If discharged within 30 days,	Yes	7 (14)

re-admission necessary after discharge	No	41 (84)
	Unknown	1 (2)
If discharged within 30 days, urinary catheter at time of discharge?	Yes	11 (22)
	No	38 (78)
	Unknown	0 (0)

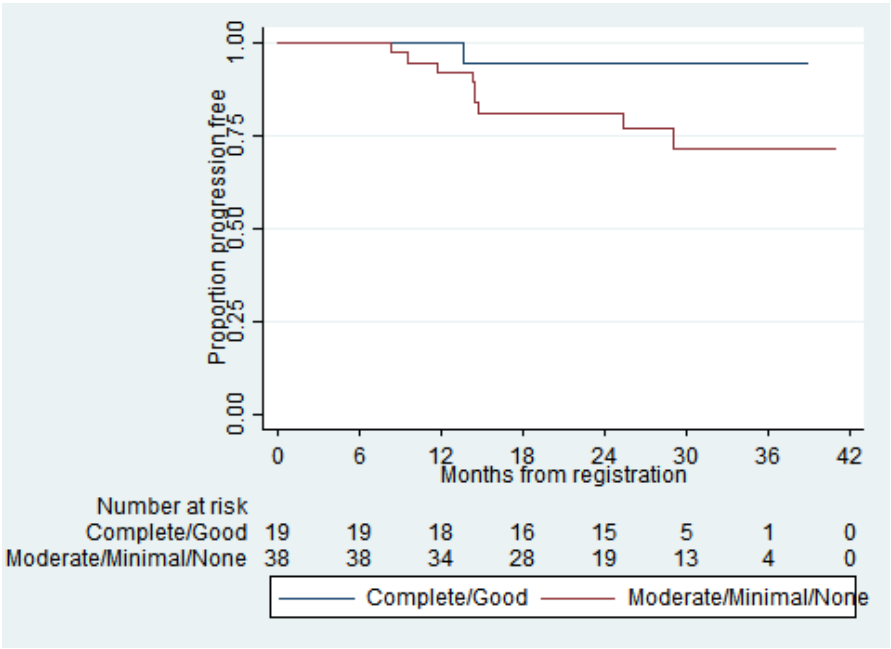
Table 4. Surgery and pathology

		n (%)*
Surgical procedure	Abdominoperineal resection	11 (19)
	Anterior resection	42 (74)
	Hartmann's	3 (5)
	Anterior resection & Prophylatic TAH & BSO	1 (2)
Does the patient have a defunctioning stoma	Yes	43 (75)
	No	11 (19)
	Missing	3 (5)
If yes, what type?	Ileostomy	32 (74)
	Colostomy	10 (23)
	Missing	1 (2)
If yes, intention?	Temporary	29 (67)
	Permanent	14 (33)
	Missing	0 (0)
Post-operative pathology	T0	7 (12)
	T1	3 (5)
	T2	19 (32)
	T3a	8 (13)
	T3b	9 (15)
	T3c	8 (13)

	T4a	1 (2)
	N0	39 (65)
	N1	13 (22)
	N2	5 (8)
	R0	56 (93)
	R1	0 (0)
Number of lymph nodes examined	Median (IQR,range,n)	19 (14-25,1-48,57)
Number of lymph nodes positive	0	39 (65)
	1-2	11 (18)
	3-5	6 (10)
	13	1 (2)
Extramural vascular invasion	Yes	11 (18)
	No	46 (77)
Distance to CRM (mm)	Number of patients who had surgery and >T0 pathology	50 (83)
Distance to CRM (mm)	Median (IQR,range,n)	12 (6-15.5,1-50,47)
pTRG	No regression	7 (12)
	Minimal regression	17 (28)
	Moderate regression	14 (23)
	Good regression	12 (20)
	Complete regression	7 (12)
	Unknown	0 (0)
Plane of resection of mesorectum	Muscularis propria	2 (3)
	Intramesorectal	6 (10)
	Mesorectal	42 (70)
	Missing	7 (12)
Plane of abdomnio-	Sphincteric	5 (46)

perineal excision**	Levator	3 (27)
	Missing	3 (27)
Distance of tumour to distal surgical margin (mm)	Median (IQR,range,n)	30 (20-50,5-100,48)
Involvement of distal margin?	No	54 (90)
	Missing	3 (5)
Distance of tumour to proximal surgical margin (mm)	Median (IQR,range,n)	182.5 (120-255,50-460,46)
Involvement of proximal margin?	No	53 (88)
	Missing	4 (7)
Is there any evidence of tumour perforation?	Yes	2 (3)
	No	53 (88)
	Unknown	2 (3)
Is there any evidence of bowel perforation?	Yes	2 (3)
	No	53 (88)
	Unknown	2 (3)
Peritoneal involvement?	Yes	1 (2)
	No	50 (83)
	Missing	6 (10)
Biopsy TCD	Median (IQR,range,n)	37.2 (22.7-44.2,6.3-58.5,59)
Resection greatest TCD	Median (IQR,range,n)	21.4 (2.7-39.1,0-59.9,57)
Resection lumenal TCD	Median (IQR,range,n)	17.6 (2.7-34.4,0-59.9,57)
Resection whole TCD	Median (IQR,range,n)	8.7 (1.3-16.1,0-38.2,57)
Resection whole TCD as % of biopsy TCD	Median (IQR,range,n)	19.4 (3.2-53.8,0-468.9,57)

Figure 3. Kaplan-Meier curve of PFS (months) by TRG



CONCLUSION:

This is the first trial to report on administration of NACT prior to SCPRT then immediate surgery in operable rectal cancer. Delivery of 8 weeks of OxMdG prior to SCPRT then surgery within a short time interval is feasible with good compliance and promising efficacy. The UK NCRI Colorectal CSG intend to include a similar NACT regimen in a forthcoming phase III trial in a similar stage of patients.

Date of the report: 14th June 2017