Research Article

A Phase I/ II Feasibility Study of Intravenous Cetuximab in Combination with 5 days Weekly Oral Capecitabine and Preoperative Radiotherapy in Rectal Cancer (XERXES)

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Abstract

Background

Preoperative Long-course chemoradiation (LCCRT) is the standard-of-care in locally advanced rectal cancer (LARC). This phase I/II trial in two sequential studies aimed to evaluate the activity and safety of the anti-epidermal growth factor receptor (EGFR) monoclonal antibody cetuximab administered weekly-prior to, and following LCCRT.

Patients and Methods

All patients had magnetic resonance imaging (MRI) defined cT3/cT4 or node-positive rectal adenocarcinoma and treatment with LCCRT (capecitabine 825 mg/m^2 bid on Monday-Friday for 5 weeks during radiotherapy [45Gy in 25 daily fractions] followed by total mesorectal excision (TME). In Phase I patients received weekly induction cetuximab 400mg/m^2 loading, then 250mg/m^2 once weekly for 4 weeks prior to standard LCCRT. In phase II 10 patients were randomised to receive: arm A standard LCCRT alone or arm B (sandwich) LCCRT with additional induction cetuximab 250mg/m^2 weekly prior to LCCRT and consolidation for 5 weeks following.

Results

In Phase I all 12 patients proceeded to surgery with a single pCR (8%) reported. This pCR rate together with acceptable compliance (100%) and toxicity (4 Grade 3 toxicities, 2 skin rash, 1 pain and 1 pulmonary embolus) and the absence of severe surgical complications allowed continuation to phase II.

In Phase II, 10 patients were recruited and five patients were randomly assigned to each treatment arm. One additional patient allocated cetuximab/CRT chose to withdraw from the trial and received no treatment. In Arm B 4/5 patients proceeded to surgery with one pCR compared to three of five patients proceeding to surgery with two achieving pCR in Arm A. The Trial closed after studies in metastatic disease reported efficacy depended on selection according to K-RAS/NRAs mutational status.

Conclusions: In unselected patients without enrichment according to KRAS/NRAS/BRAF status, the addition of induction and consolidation cetuximab to pre-operative LCCRT provided modest efficacy with good compliance and manageable toxicity.

Introduction

Randomized phase III trials have confirmed that preoperative long-course chemoradiation (LCCRT) with concurrent fluoropyrimidines significantly reduces local recurrence in LARC and is now the standard of care [1,2]. Yet, not all patients respond, and achieving better local control has not impacted on the frequency of metastases and disease-free (DFS) or overall survival (OS) [3,4]. Hence, investigators have aspired both to enhance radio-sensitivity and to target potential micrometastases early by integrating additional neoadjuvant cytotoxic and molecularly-targeted treatments into LCCRT. This strategy also aims to increase down-staging and pathological complete response (pCR) rates, thereby potentially avoiding radical surgery with a 'watch and wait' management.

Integration of additional cytotoxic agents into standard LCCRT regimens has often been accompanied by excess acute toxicity with minimal increases in efficacy. Randomized phase III trials (STAR-01,

ACCORD 12/0405-Prodige2, NSABP R-04) evaluated the addition of oxaliplatin into preoperative fluoropyrimidine-based LCCRT [5-8], but failed to increase pCR rates or impact on survival**.** Although the German CAO/ARO/AIO-04 study showed a significant increase in pCR and an improvement in DFS [8].

Epidermal growth factor receptor (EGFR) is over-expressed in approximately 50%-80% of rectal cancers, and is associated with a poor prognosis [9] conferring relative resistance to both chemotherapy and radiotherapy [10,11], and worse survival. Since EGFR-targeted monoclonal antibodies are effective in metastatic colorectal cancer (mCRC) and significantly prolong PFS [12,13], investigators have examined the addition of EGFR targeted therapies in combination with LCCRT in LARC. The molecular rationale has been previously reviewed in depth [14].

Cetuximab is a chimeric immunoglobulin G1 monoclonal antibody directed against EGFR, which is responsible for cell differentiation, proliferation, and survival. Pre-clinical studies demonstrate hypoxia may upregulate EGFR [15]. Landmark trials in squamous cell cancer of the head and neck (SCHN) showed the addition of cetuximab combined with radiotherapy, improved both loco-regional control and median OS [16] compared to patients who received radiation alone.

Early clinical studies in rectal cancer provided inconsistent response results for EGFR expression and cetuximab and radiation [9,11,17]. Phase I trials demonstrated an acceptable toxicity profile (Grade 3 diarrhoea in 15–20%) but no obvious increase in down-staging [18,19].

Early efficacy endpoints, such as pCR rates appear lower when EGFR antibody was added to standard LCCRT with capecitabine/5-FU alone [19-21] or combined with irinotecan or oxaliplatin [22-24].

A subsequent randomised phase II study of cetuximab and 5-FU chemoradiation, showed similar pCR rates for patients in the cetuximab arm to patients on the standard LCCRT control arm without cetuximab [25]. Even when analysed for KRAS wild-type participants, studies showed no difference in PCR rates or outcomes [26-28]. Hence, the benefit of cetuximab in addition to concurrent single or doublet chemotherapy in rectal cancer CRT remains uncertain.

Hence, the integration of cetuximab as consolidation was proposed after the completion of LCCRT in the interval before surgery [22]. Other investigators also suggested efficacy of radiation might be enhanced by cetuximab-induced inhibition of repopulation during the latter phase of radiotherapy [29].

This present study aimed to investigate the strategy of the addition of induction, concurrent and consolidation cetuximab to capectabine-based LCCRT in a phase I/ II sequential study. However, accumulating evidence of poor efficacy (in terms of pCR) and in light of the widely held hypothesis that cetuximab can lead to G1 or G2/M cell cycle arrest, the phase II protocol was amended to examine a novel cetuximab induction and consolidation ‘sandwich’ approach to avoid concurrent administration.

Materials and Methods

Trial Design

In this multicentre sequential study we conducted a phase I study followed by a randomised phase II study. Both studies were approved by the local ethical committee and registered (EudraCT 2004-001926-26). For the Phase I trial patients were recruited between December 2005 and November 2006, and in the Phase II patients were recruited between July 2011 and October 2012.

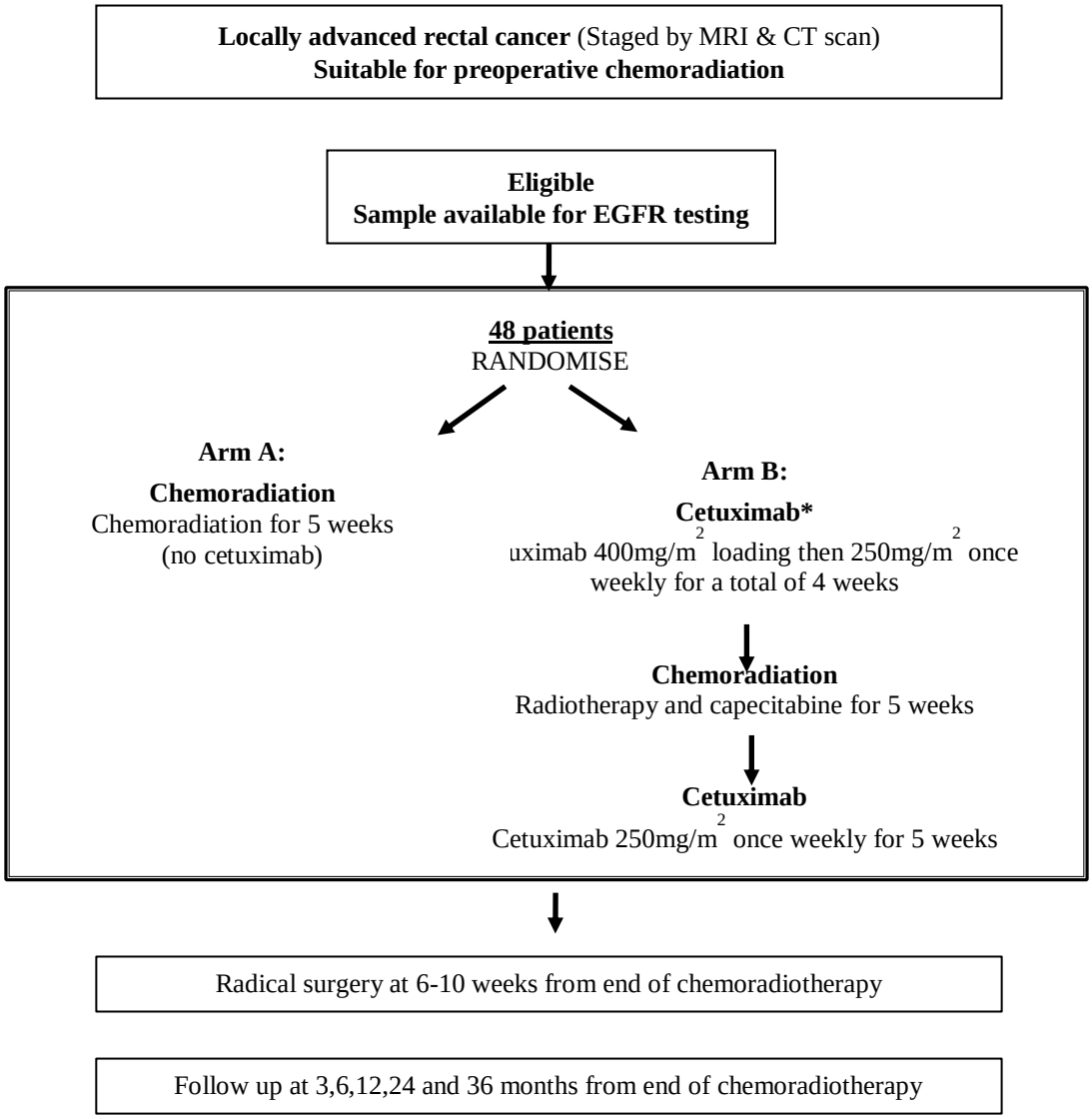
The primary endpoint according to protocol for both phases was the pCR rate, acute toxicity compromising compliance to radiotherapy and chemotherapy. Secondary endpoints included histological down-staging, R0 (circumferential resection margin [CRM] >1 mm) resection rate, and surgical complications.

The design aimed to recruit 12 patients into the phase I study, who were to receive induction cetuximab followed by standard chemoradiotherapy with concurrent capecitabine. On the basis of achieving a pCR of 8% and adequate compliance and safety then a further 48 patients would be recruited to a randomised phase II trial. Initially we planned to allocate patients to standard capecitabine based LCCRT or a novel arm of induction cetuximab followed by cetuximab concurrent with radiotherapy and capecitabine. This 2-step Fleming design also allowed indirect comparison of the original Phase I strategy of synchronous cetuximab with a sandwich approach.

Although the findings from the phase I trial met the criteria for continuing to Phase II the Trial Management Group was aware of emerging data. Karapetis et al showed responses to cetuximab occur exclusively in patients without activating mutations in codon 12 and 13 of KRAS [30] and we were aware of disappointing data in terms of low pCR achieved when cetuximab was added concurrently to LCCRT.

The design of our Phase II trial was amended. In the revised design patients were randomly assigned in a 1:1 ratio to a standard treatment arm A (radiotherapy and capecitabine without cetuximab) or to receive weekly induction cetuximab x 4 before and after capecitabine LCCRT (but not concurrently) in Arm B. (Figure 1). There were no stratification factors.

This study is registered at controlled-trials.com, number 26715889.



**Tumour biopsies to be taken 4 hrs after first cetuximab infusion and in week 4*

Figure 1: Original Planned Trial Consort Diagram

Patients

Eligible patients had histologically proven adenocarcinoma of the rectum (<15cm from anal verge) with sufficient tumour available for testing of EGFR status. The indications for pre-operative chemoradiotherapy demanded either partially fixed/unresectable disease or locally advanced disease (cT3/cT4) where the preoperative MRI confirms the unlikelihood of an R0 resection. MRI was mandated to define tumour either beyond mesorectal fascia, ≤ 2mm from mesorectal fascia or T3/T4 tumour ≤5cm from the anal verge.

Additional eligibility criteria included WHO performance status of <2, no distant metastases, age ≥ 18 years, no prior chemotherapy or radiotherapy, neutrophil count ≥1,500/µL, platelet count ≥100.000/µL, serum creatinine <1.5x upper limit of normal (ULN) GFR ≥50ml/min, alanine aminotransferase or aspartate aminotransferase ≤2.5xULN, serum ALP <5xULN, serum bilirubin <2xULN, no concurrent uncontrolled medical condition likely to compromise the delivery of chemotherapy or radiotherapy, and signed written informed consent.

Baseline evaluation required clinical history, physical examination (including digital rectal examination), recording of concomitant medication, laboratory tests (hematology and clinical chemistry, carcinoembryonic antigen) (CEA), biopsy, MRI of pelvis, and X-ray or (computed tomography) CT of chest and CT of abdomen and pelvis.

Procedures

LCCRT: In both trial phases radiation was conformally planned using computerised tomography (CT) using 45 Gy in 25 fractions over 33 days and encompassing the primary tumour and pelvic lymph nodes. Concomitant capecitabine was taken by mouth at 825 mg/m^2 twice daily d on Monday-Friday for each week for 5 weeks on the days of radiotherapy. Dose adjustment was made according to observed toxicity, assessed using National Cancer Institute Common Terminology Criteria for Adverse Events version 4.0 and Radiation Therapy Oncology Group score 1 to 4.

Phase I: LCCRT and cetuximab by IV infusion at a loading dose of 400 mg/m^2 and subsequently at 250 mg/m^2 weekly for 4 weeks only prior to the start of LCCRT.

Phase II: Patients were randomised to Arm A LCCRT as described above or Arm B cetuximab by IV infusion at the doses described for Phase I and 250 mg/m^2 weekly for 5 weeks following LCCRT.

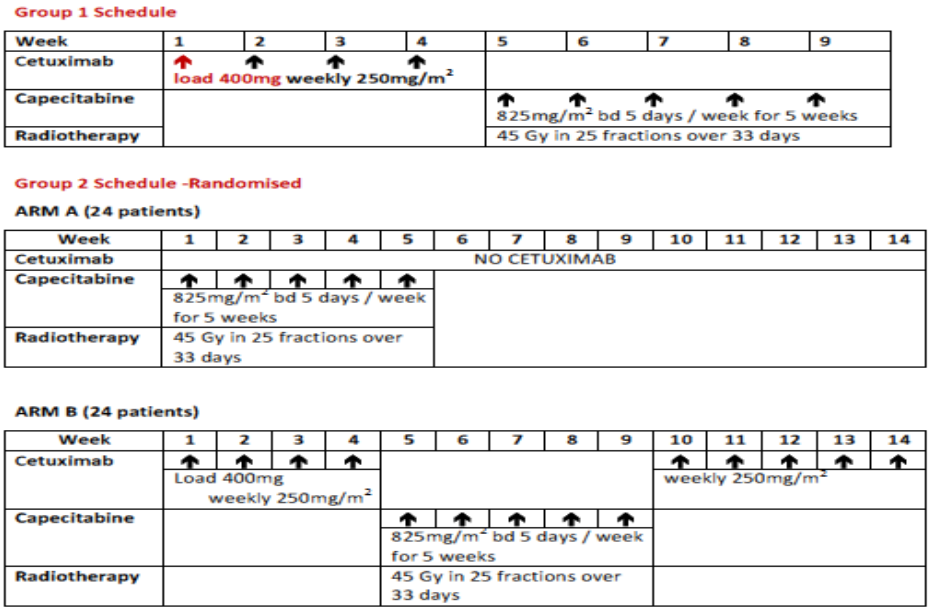


Figure 2: Planned schema of the original planned sequential

Post Chemoradiation Procedures

Response: A preliminary assessment of efficacy, in terms of objective tumour response was planned using CT and/or MRI scanning 5-9 weeks after completion of treatment.

Further Treatments: Total mesorectal excision (TME) was intended to be performed 6- 10 weeks after completion of CRT, unless post-chemoradiation imaging demonstrated inoperable/unresectable tumour or metastatic disease. Postoperative adjuvant chemotherapy (4 months) was at the discretion of the investigator and if proposed, was planned to commence 6 to 10 weeks after surgery. The protocol did not mandate either 5FU alone of oxaliplatin based chemotherapy.

Follow-up: Follow-up in clinic with CEA measurements every 3 months in year 1, every 6 months in years 2 and 3, and annually in years 4 and 5 was recommended. A CT scan of the thorax, abdomen, and pelvis was performed at 12, 24, and 36 months, and an MRI of the pelvis was performed at 24 months.

Endpoint Measurements and Data Analysis

The primary endpoint was pathological complete response-defined as the absence of any residual tumour cells detected in the resected specimen in both primary tumor and lymph nodes (ypT0N0). Tumor down-staging was identified by comparison of the baseline clinical TNM stage and the histopathological stage A radical resection (R0) was defined as the removal of all macroscopic tumor with no evidence of distant metastases, the absence of microscopic residual tumor, and uninvolved resection margins. Resection specimens were examined for margin involvement, which was defined as tumour observed ≤ 1 mm from the margins of the surgical specimen. Specimens are classified using a tumor regression grade (TRG) proposed by Dworak et al [31].

The acute toxicity of the combined therapy focussed on gastrointestinal effects in terms of acute diarrhoea, nausea and vomiting, and haematological parameters, with special reference to grade 3 and 4 toxicities which compromise compliance to radiotherapy. Other secondary end points included, surgical complications at 1 month, compliance with the planned dose of capecitabine and radiotherapy.

Statistical Analysis/Sample Size

No formal sample calculation was done for the phase 1b design. The sample size required for the phase II study was based on a Fleming single stage design [32]. It was assumed that the pCR rate in historical controls was 8%. With an 80% power and 5% one sided significance level, 24 patients were required to detect an expected pCR rate of >=25% in the cetuximab 'sandwich' regimen. Therefore, if at least 5 patients achieved pCR, then this would be seen as sufficient to warrant further investigation of this regimen. A non-comparative randomised design was added to this study to allow a descriptive comparison between the experimental regimen and the control group and therefore a further 24 patients were randomised to a control group.

Results

Pre-treatment characteristics for both trials are shown in Table 1, confirming these were locally advanced cancers according to MRI criteria, and that they were well balanced in the randomised phase II.

In the phase I trial, compliance to capecitabine in LCCRT was excellent with no reductions for toxicity. Compliance to cetuximab was also acceptable. One patient stopped cetuximab with toxicity, and two patients had a delay (one for administrative reasons). Compliance to irradiation was acceptable (Table 2).

All 12 patients enrolled in the phase I proceeded to surgery with a single pCR (8%) reported. With a median follow-up of 42 months, five patients recurred (liver (1), lung (1), brain (1), loco-regional and spleen (1) and loco-regional/nodal/lung (1) and 3 patients died due to rectal cancer; 1 patient died due to Rectal cancer + Chemo related SAE (Renal Failure and Pneumonia).

In the randomised phase II, 10 patients were recruited and randomly assigned to Group A (5) and group B (5) before the early closure of the trial on 11th September 2012. This was on the recommendation of the Trial steering Committee due to emerging data from other phase II trials reporting on selection for cetuximab according to KRAS mutation status. One patient allocated cetuximab/CRT chose to withdraw from the trial and received no treatment. Hence the analysis is based on 9 patients.

In the phase II a range of adverse events were reported at Grade 3 and below (Table 3). There were no G4/G5 events. All 4 patients who received cetuximab in Arm B experienced an acneiform rash. A single patient in arm A (Capecitabine/CRT) experienced a grade 3 diarrhoea episode in week 5.

Compliance to capecitabine and cetuximab and LCCRT was good but only 7 patients proceeded to surgery (1 declined, 1 deemed too unfit). Compliance to capecitabine was similar between the 2 arms and no patient stopped capecitabine permanently. A single patient had a delay to starting cetuximab. Radiotherapy compliance was also excellent, all patients received 25 planned fractions, although 4 patients had delays (administrative reasons (2), intercurrent illness (1) and toxicity (1).

One of 5 patients in the control arm and 2 of 3 in the cetuximab arm achieved a pCR (3/10 on ITT and 3/7 who underwent surgery). There was no statistical difference between the two arms with respect to the rates of R0 resection, sphincter-sparing surgery, or surgical complication (although numbers are clearly small). None of the 7 patients who underwent surgery had an anastomotic leak. With a median follow-up of 38 months, there were 2 recurrences (both lung) one of whom subsequently died.

Table 1: Baseline characteristicsof Phase I and Phase II trial participants

Baseline Characteristics	**Phase Ib**	**Phase II**	
	N=12 N (%)	Arm A (Capecitabine and radiotherapy) N=5	Arm B (Cetuximab, capecitabine and radiotherapy) N=5
Sex			
Female	1 (8%)	2 (40%)	2 (40%)
Male	11 (92%)	3 (60%)	3 (60%)
Age (years) Median (range)	65 (29-76	62 (57- 78)	63 (54-69)
WHO performance status			
0	7 (58%)	3 (60%)	4 (80%)
1	5 (42%)	2 (40%)	0 (0%)
Not reported for WHO performance status	0 (0%)	0 (0%)	1 (20%)
Tumour stage (T3/T4)			
T2	0 (0%)	1 (20%)	1 (20%)
T3	9 (75%)	3 (60%)	3 (60%))
T4	3 (25%)	1 (20%)	1 (20%)
Tumour stage			
Tumour beyond mesorectal fascia	3 (25%)	1 (20%)	0 (0%)
Tumour ≤ 2mm from mesorectal fascia	5(42%)	1 (20%)	1 (20%)
T3/T4 tumour ≤ 5cm from the anal verge	7 (58%)	3 (60%)	4 (80%)
Nodal status			
N0	2 (17%)	0 (0%)	1 (20%)
N1	4 (33%)	4 (80%)	2 (40%)
N2	4 (33%)	1 (20%)	2 (40%)
NX	2 (17%)		
Site			
Lower (0- 4.9 cm)	4 (33%)	2 (40%)	2 (40%)
Middle (5- 9.9cm)	7 (58%)	3 (60%)	2 (40%)
Upper (10- 15cm)	1 (8%)	0 (0%)	1 (20%)
Baseline CEA (µg/l) Median (range)	3 (1- 45)	2 (1 to 20)	2.2 (1 to 8)

Table 2: Radiotherapy Compliance

Radiotherapy Compliance	**Phase I**	**Phase II**	
	N=12 N (%)	Arm A (Capecitabine and radiotherapy) N=5	Arm B (Cetuximab, capecitabine and radiotherapy) N=5
Number of patients who had radiotherapy	12 (100%)	5 (100%)	4 (80%)
Total dose given at ICRU reference			
45	12 (100%)	5 (100%)	4 (100%)
Number of Fractions			
25	12 (100%)	5 (100%)	4 (100%)
Irradiation temporarily interrupted			
Yes	1 (8%)	3 (60%)	1 (25%)
No	11 (92%)	2 (40%)	3 (75%)
Reasons for irradiation temporarily interrupted			
Bank holiday	1 (8%)	1 (20%)	1 (25%)
Intercurrent Illness	0 (0%)	1 (20%)	0 (0%)
Toxicity	0 (0%)	1 (20%)	0 (0%)
Irradiation stopped early			
No	12 (100%)	5 (100%)	4 (100%)
Yes	0 (0%)	0 (0%)	0 (0%)

Table 3: Worst adverse event experienced during the study

CTCAE term 4.0	**Arm A (Capecitabine and radiotherapy) N=5**		**Arm B (Cetuximab, capecitabine and radiotherapy) N=4**	
	Grade 1 & 2	Grade 3	Grade 1 & 2	Grade 3
Blood and lymphatic system disorders				
Anemia	2 (40%)	.	1 (25%)	.
Any Blood and lymphatic system disorders	2 (40%)	.	1 (25%)	.
Ear and labyrinth disorders				
Other Ear and labyrinth disorders	1 (20%)	.	.	.
Any Ear and labyrinth disorders	1 (20%)	.	.	.
Eye disorders				
Blurred vision	.	.	1 (25%)	.
Eye pain	1 (20%)	.	.	.
Other eye disorders	1 (20%)	.	.	.

CTCAE term 4.0	**Arm A (Capecitabine and radiotherapy) N=5**		**Arm B (Cetuximab, capecitabine and radiotherapy) N=4**	
	Grade 1 & 2	Grade 3	Grade 1 & 2	Grade 3
Any Eye disorders	1 (20%)	.	1 (25%)	.
Gastrointestinal disorders				
Diarrhea	3 (60%)	1 (20%)	3 (75%)	.
Anal haemorrhage	.	.	1 (25%)	.
Anal pain	1 (20%)	.	2 (50%)	.
Constipation	2 (40%)	.	5 (50%)	.
Mucositis oral	2 (40%)	.	1 (25%)	.
Nausea	2 (40%)	.	3 (75%)	.
Oral pain	.	.	1 (25%)	.
Proctitis	.	.	1 (25%)	.
Rectal pain	2 (40%)	.	2 (50%)	.
Vomiting	1 (20%)	.	.	.
Any Gastrointestinal disorders	3 (60%)	1 (20%)	4 (75%)	.
General disorders and administration site conditions				
Fatigue	5 (100%)	.	4 (100%)	.
Non-cardiac chest pain	1 (20%)	.	.	.
Pain	1 (20%)	.	1 (25%)	.
Any General disorders and administration site conditions	5 (100%)	.	4 (100%)	.
Immune system disorders				
Allergic reaction	.	.	1 (25%)	.
Any Immune system disorders	.	.	1 (25%)	.
Infections and infestations				
Nail infection	.	.	1 (25%)	.
Other infection	.	.	1 (25%)	.
Paronychia	.	.	1 (25%)	.
Any Infections and infestations	.	.	1 (25%)	.
Injury, poisoning and procedural complications				
Dermatitis radiation	2 (40%)	.	2 (50%)	.
Any Injury, poisoning and procedural complications	2 (40%)	.	2 (50%)	.
Investigations				
Alanine aminotransferase increased	2 (40%)	.	1 (25%)	.
Aspartate aminotransferase increased	2 (40%)	.	.	.
GGT increased	3 (60%)	.	1 (25%)	.
Neutrophil count decreased	1 (20%)	.	2 (50%)	.

CTCAE term 4.0	**Arm A (Capecitabine and radiotherapy) N=5**		**Arm B (Cetuximab, capecitabine and radiotherapy) N=4**	
	Grade 1 & 2	Grade 3	Grade 1 & 2	Grade 3
Other Investigations	.	.	1 (25%)	.
White blood cell decreased	1 (20%)	.	1 (25%)	.
Any Investigations	4 (80%)	.	3 (75%)	.
Metabolism and nutrition disorders				
Anorexia	2 (40%)	.	2 (50%)	.
Hypermagnesemia	1 (20%)	.	.	.
Hypoalbuminemia	2 (40%)	.	1 (25%)	.
Any Metabolism and nutrition disorders	3 (60%)	.	2 (50%)	.
Musculoskeletal and connective tissue disorders				
Pain in extremity	1 (20%)	.	.	.
Any Musculoskeletal and connective tissue disorders	2 (40%)	.	1 (25%)	.
Nervous system disorders				
Dizziness	1 (20%)	.	.	.
Dysgeusia	.	.	2 (50%)	.
Headache	.	.	2 (50%)	.
Peripheral sensory neuropathy	.	.	1 (25%)	.
Any Nervous system disorders	1 (20%)	.	3 (75%)	.
Psychiatric disorders				
Anxiety	.	.	1 (25%)	.
Confusion	1 (20%)	.	.	.
Any Psychiatric disorders	1 (20%)	.	1 (25%)	.
Renal and urinary disorders				
Cystitis noninfective	1 (20%)	.	.	.
Other Renal and urinary disorders	1 (20%)	.	2 (50%)	.
Renal and urinary disorders - dysuria	1 (20%)	.	1 (25%)	.
Any Renal and urinary disorders	3 (60%)	.	3 (75%)	.
Respiratory, thoracic and mediastinal disorders				
Dyspnea	2 (40%)	.	1 (25%)	.
Epistaxis	.	.	1 (25%)	.
Sore throat	1 (20%)	.	.	.
Any Respiratory, thoracic and mediastinal disorders	3 (60%)	.	2 (50%)	.
Skin and subcutaneous tissue disorders				
Dry skin	2 (40%)	.	1 (25%)	.
Pain of skin	.	.	1 (25%)	.

CTCAE term 4.0	**Arm A (Capecitabine and radiotherapy) N=5**		**Arm B (Cetuximab, capecitabine and radiotherapy) N=4**	
	Grade 1 & 2	Grade 3	Grade 1 & 2	Grade 3
Palmar-plantar erythrodysesthesia syndrome	1 (20%)	.	1 (25%)	.
Rash acneiform	.	.	4 (100%)	.
Scalp pain	.	.	2 (50%)	.
Skin and subcutaneous tissue disorders - Brittle Nails	.	.	1 (25%)	.
Any Skin and subcutaneous tissue disorders	3 (60%)	.	4 (100%)	.
Vascular disorders				
Hypotension	.	.	1 (25%)	.
Any Vascular disorders	.	.	1 (25%)	.
Any Adverse event	**4 (80%)**	**1 (20%)**	**4 (100%)**	**.**

Note: There was no reported grade 4 and 5 adverse events. Patient 2 [Arm A (Capecitabine and radiotherapy)] was the patient who had a grade 3 diarrhoea episode in week 5. (it does not include AE reported in the baseline visit; it includes any adverse reported during the study including surgery and follow-up visits; it includes late toxicity).

Discussion

Despite limited numbers, this study showed that a strategy of induction and consolidation cetuximab (without concurrent delivery with radiation) is feasible. The acute toxicity of this cetuximab 'sandwich' approach was low. The strategy was associated with good compliance to LCCRT and no excess of surgical morbidity. The pCR rate was 1/12 (8%) in Cohort 1 and 2/3 (66%) in the cetuximab arm of Cohort 2. Although in the majority of studies the addition of cetuximab to preoperative CRT achieved similar results in terms of pCR compared with chemoradiation alone, and does not suggest radio-sensitization is occurring.

The strength of our analysis is that patients were treated in the framework of prospective studies, with rigorous protocol requirements for treatment and follow-up. The limitations include the small numbers in each cohort, and the fact that the phase II component was not blinded either to patients or healthcare professionals. The results are useful only for hypothesis generating. In addition, this study was designed prior to knowledge regarding resistance to cetuximab in RAS-mutant tumours treated within mCRC chemotherapy schedules [33]. Approximately 40% of rectal cancers show activating K-RAS mutations. Due to the frequency and therapeutic implications of this mutation, *KRAS* testing has now been incorporated into routine clinical practice as part of the treatment for metastatic CRC. The present trial population was unselected for RAS and NRAS-wild-type tumours. Preclinical studies of cetuximab concurrent with radiotherapy initially suggested the

KRAS mutation would confer resistance to radiotherapy in patients with rectal cancer, but clinical analyses are inconsistent in terms of achieving pCR [34,35]. None of the early studies selected patients to enrich their population according to K-RAS status [36-38], so our knowledge is founded on retrospective analyses. In the only sizeable randomized phase II trial (EXPERT-C), the addition of cetuximab both to induction neoadjuvant chemotherapy (CAPOX) and to capecitabine CRT did not significantly enhanced the pCR rate (18% vs 15%), even in the subgroup with RAS/BRAF wild-type tumours. A meta-analysis of studies which integrated cetuximab into fluoropyrimidine based LCCRT schedules, suggested the presence or absence of K-RAS mutations in the tumour does not impact on pCR rates [39]. Mutations in different KRAS codons may have different effects – possibly reflecting the frequency of additional TP53 mutations in KRAS mutant tumors [40]. Other synchronous mutations such as TP53 may also influence response and outcomes [41].

Phase I-II trials suggest the addition of cetuximab to chemoradiation with fluoropyrimidines (and additional oxaliplatin or irinotecan) was usually associated with increased toxicity in terms of diarrhoea and did not significantly increase pCR rates, nor improve survival. The lack of significant improvement in efficacy with the addition of cetuximab to preoperative capecitabine and radiotherapy remains poorly explained.The original schedule employed by Bonner in SCCHN started cetuximab one week before radiotherapy with a loading dose of 400 mg/m2 and continued with weekly infusions of 250 mg/m2 concurrently for the duration of radiotherapy [16]. Most investigators have copied this schedule. A few have investigated neoadjuvant induction chemotherapy (Capeox and cetuximab) followed by cetuximab concurrent with LCCRT [24,42], but we are unaware of any other studies using neoadjuvant cetuximab as consolidation after LCCRT.

Our novel ‘sandwich’ schedule should be investigated. Preclinical data suggests that consolidation cetuximab following chemotherapy or radiotherapy is a more logical strategy than induction. Radiotherapy cell kill is enhanced in xenografts [43], although these cell lines had intact wild-type p53. Given that cetuximab, has a long half-life (approximately 97-114 h) and G1 arrest is associated with EGFR inhibition [36] redistribution of tumor cells to a more radiosensitive phase of the cell cycle may be blocked by induction and concurrent administration of cetuximab.

Cetuximab as consolidation is also more effective if sequenced after chemotherapy than before [44]. Cetuximab consolidation following LCCRT may therefore inhibit LCCRT- induced signalling (AKT/ERK) and impair DNA repair [14] and provide an adverse local microenvironment. We could find only a single trial examining consolidation cetuximab and this followed following concurrent cetuximab, performed in non-small-cell lung cancer [45]. We could find no other studies in rectal cancer.

Table 4: Results: Surgical details amongst patients who had surgery.

	Phase IB	**Phase II**	
Surgery outcomes	**N=12 N (%)**	**Arm A (Capecitabine and radiotherapy) N=4**	**Arm B (Cetuximab, capecitabine and radiotherapy) N=3**
Operation type			
AP resection	7 (58%	2	1
Anterior resection	5 (42%)	4	2
Complete clinical response			
Yes	1 (8%)	3	1
No	11 (92%)	1	2
yR stage			
R0	8 (67%)	4	1
R1	1 (8%)	0	2
R2	1 (8%)		
Not reported	2 (17%)		
Regression			
No tumour present	1 (8%)	1	2
Few tumour cells	3 (25%)	1	1
Moderate	2 (17%)	1	0
Mild	4 (33%)	1	0
Unknown	2 (17%)		

pCR total ITT 4/22 (18%)

pCR total per-protocol 4/19 (21%)

pCR in those who received cetuximab 3/17 (18%)

Conclusion

Our understanding of the interaction of RAS wild-type tumours combined with radiotherapy and concurrent capecitabine, Irinotecan or Oxaliplatin remains imperfect. Multiple biologically targeted therapies have been examined in phase I/II trials in LARC, but none have succeeded in demonstrating sufficient additional efficacy compared with standard fluoropyrimidine –based LCCRT. There are no convincing data to support the use of targeted agents against EGFR combined with LCCRT. Although our study was unable to recruit as intended, the novel 'sandwich' schedule using a standard capecitabine based LCCRT delivered between induction and consolidation weekly cetuximab was not associated with the decreased efficacy as described in concurrent

schedules. Acute toxicity and compliance also appeared acceptable. Hence, this strategy could be a way forward in the future and needs further exploration.

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