CRITICS II

A MULTICENTRE RANDOMISED PHASE II TRIAL OF NEO-ADJUVANT CHEMOTHERAPY FOLLOWED BY SURGERY VS. NEO-ADJUVANT CHEMOTHERAPY AND SUBSEQUENT CHEMORADIOTHERAPY FOLLOWED BY SURGERY VS. NEO-ADJUVANT CHEMORADIOTHERAPY FOLLOWED BY SURGERY IN RESECTABLE GASTRIC CANCER

ANTONI
VAN
LEEUWENHOEK
NEDERLANDS KANKER INSTITUUT

CRITICS-II

THIS STUDY IS CONDUCTED UNDER THE HEADING OF THE DUTCH UPPER GI CANCER GROUP (DUCG)

• NKI-AVL	Sponsor
• Marcel Verheij	Principal Investigator
• Edwin Jansen	Coordinator Radiation Oncology
• Hanneke van Laarhoven	Coordinator Chemotherapy
• Johanna van Sandick	Coordinator Surgery
• Nicole van Grieken	Coordinator Pathology
• Harm van Tinteren/Karolina Sikorska	Coordinator Statistics
• Pietje Muller	Coordinator data centre

DUTCH CANCER SOCIETY

DUCG
Dutch Upper GI Cancer Group

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INTRODUCTION AND RATIONALE (1)

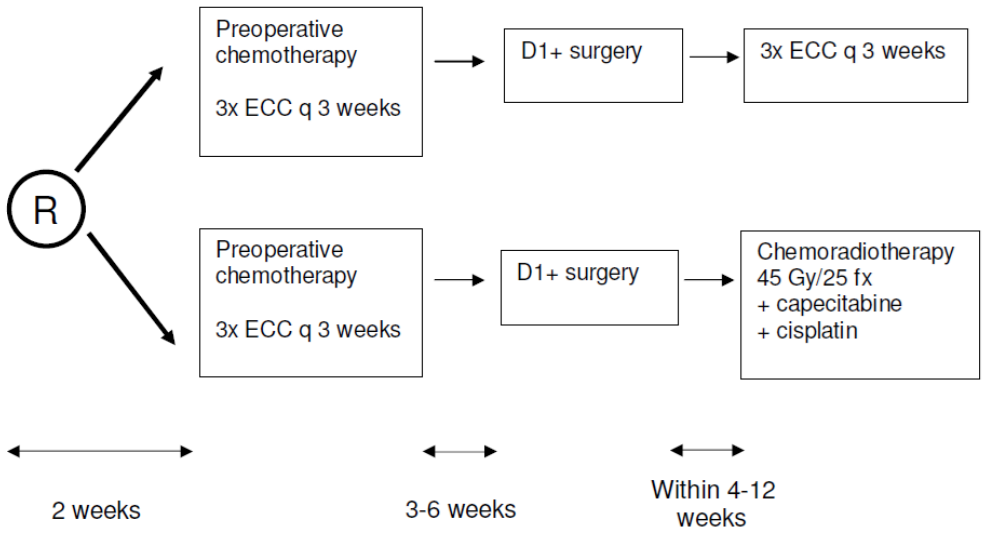
INTRODUCTION

- Radical surgical resection remains the basis of cure in gastric cancer
- Surgery alone provices long-term survival of 20-30%
- Current standard
  - D2 lymph node dissection current standard (DGCG trial)
  - Perioperative chemotherapy (MAGIC trial); or postoperative chemotherapy (CLASSIC trial); or postoperative chemoradiotherapy (SWOG/Intergroup trial)

INTRODUCTION AND RATIONALE (2)

CRITICS-I

- Randomised controlled phase III trial
- N=788



- 5-year OS was similar: 40.8% for CT and 40.9% for CRT therapy
- Median survival of 3.5 years for CT and 3.3 years for CRT.

INTRODUCTION AND RATIONALE (3)

PATIENT COMPLIENCE IN (NEO)ADJUVANT STUDIES IN GASTRIC CANCER

Studie	Behandelgroep	Behandeling afgerond (%)
SWOG	S→CRT	64%
MAGIC	CT→S→CT	42%
ACTS-GC	S→CT	66%
CLASSIC	S→CT	67%
ARTIST	S→CT	75%
	S→CRT	82%
ST03	CT→S→CT	40%
	CT+B→S→CT+B	37%
TOPGEAR part 1	CT→S→CT	58%
	CT→CRT→S→CT	45%
FLOT4-AIO	CT→S→CT (3xECF/ECX)	37%
	CT→S→CT (4xFLOT)	50%

RATIONALE

CONCEPTS

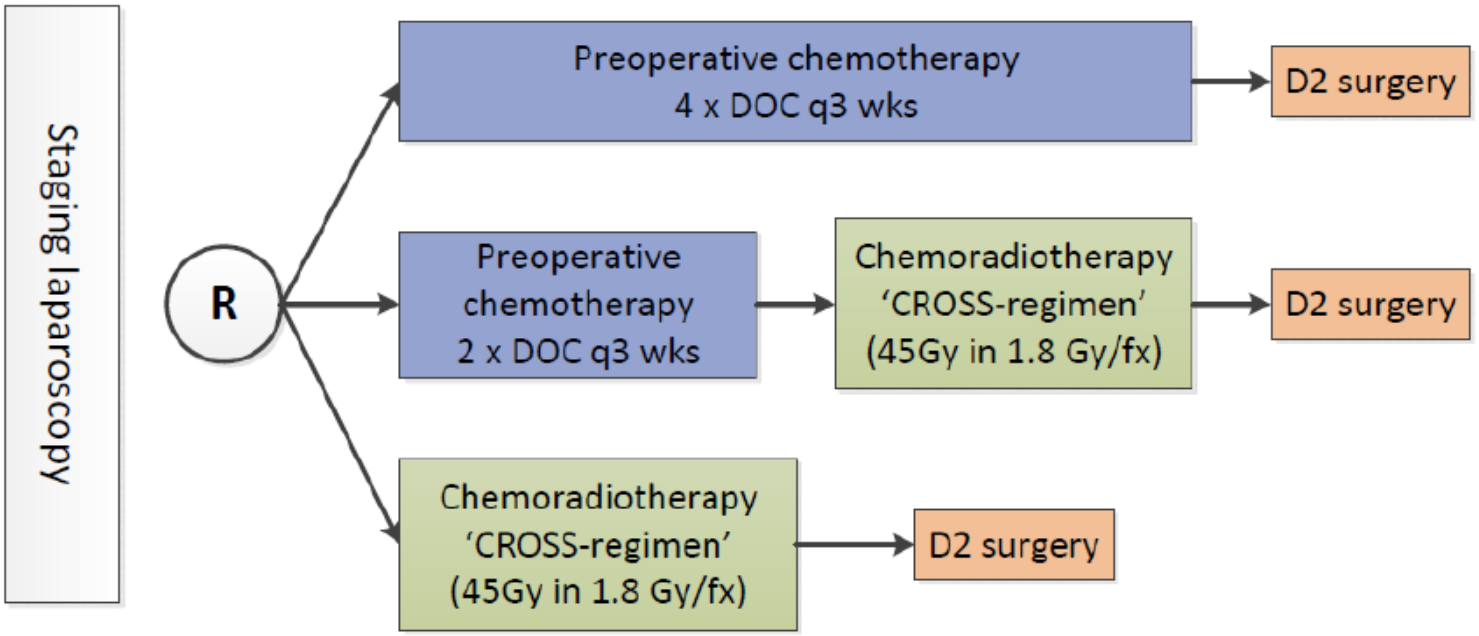
- Pre-operative treatment is associated with better patient compliance than post-operative regimens
- Pre-operative treatment increases the likelihood of disease downsizing/ downstaging and radical R0 resections
- Pre-operative paclitaxel/carboplatin-based concurrent chemotherapy and DOC chemotherapy are effective, feasible and safe regimens

AIM

- To optimize pre-operative treatment resectable gastric cancer

DESIGN

RANDOMISED CONTROLLED PHASE II TRIAL



STUDY OBJECTIVES AND ENDPOINTS (1)

PRIMARY OBJECTIVE

- To assess which preoperative regimen provides superior event-free survival at 1 year after randomisation in patients with resectable gastric cancer

  (event= local/regional recurrence or progression, distant recurrence, or death from any cause).

STUDY OBJECTIVES AND ENDPOINTS (2)

SECONDARY OBJECTIVES

- To assess time to event of all treatment arms
- To assess which preoperative regimen provides superior time-to-recurrence (TTR)
- To assess which preoperative regimen is most feasible, based on toxicity, pCR and R0 resection rates
- To assess the toxicity profile of all treatment arms
- To document surgical morbidity, including incidence of anastomotic leakage
- To determine the pCR rates of all treatment arms
- To determine the R0 resection rates of all treatment arms
- To determine the response rate (RR) of all treatment arms
- To determine the OS of all treatment arms
- To identify which preoperative regimen (CRITICS-II) will be compared with the new standard treatment (CRITICS-I) in a next phase III trial

STUDY OBJECTIVES AND ENDPOINTS (3)

EXPLORATIVE OBJECTIVES

- To assess the relationship between classical histopathological parameters with clinical outcome parameters
- To identify new biomarkers that predict clinical outcome and response to treatment
- To identify genomic changes in tumour-derived DNA circulating in plasma

NUMBER OF PATIENTS

207 PATIENTS IN TOTAL

- First stage 42 patients per arm (126 patients)
- ***Interim analysis*** *(endpoint event-free survival (Case and Morgan); response; toxicity)*
- Second stage 27 patients per arm (81 patients)

- Current inclusion n=117

POPULATION (1)

STUDY POPULATION

Patients with stage IB-IIIC (TNM **8th** ed) resectable gastric carcinoma (adenocarcinoma; histologically proven), tumour bulk has to be in the stomach but may involve gastro-oesophageal junction.

INCLUSION CRITERIA

- Performance status WHO < 2
- Age ≥ 18 yrs
- No prior radiotherapy
- Adequate hematologic status; renal function; liver function (defined in protocol)
- At staging laparoscopy **(mandatory)** obtained biopsies of suspected peritoneal lesions and/or substantial free peritoneal fluid if any should be pathologically proven tumor negative
- Written informed consent
- Expected adequacy of follow-up
- Caloric intake ≥ 1500 kcal/day, verified by a **dietician** before registration.
  - If caloric intake is < 1500 kcal/day or if bodyweight has decreased > 10% over the last 6 months or > 5% over the last month, dietary intervention such as oral nutritional support or enteral tube feeding is mandatory

POPULATION (2)

EXCLUSION CRITERIA (1)

- T1N0 disease (assessed by EUS) or distant metastasis
- Inoperable patients; due to technical surgery-related factors or general condition
- Previous malignancy, except adequately treated non-melanoma skin cancer or in-situ cancer of the cervix uteri; in case of a previous other malignancy with a disease-free period ≥ 5 years, inclusion can be accepted after consultation of the principal investigator
- Solitary functioning kidney that will be within the radiation field
- Major surgery within 4 weeks prior to study treatment start, or lack of complete recovery from the effects of major surgery
- Uncontrolled (bacterial) infections
- Significant concomitant diseases preventing the safe administration of study drugs or likely to interfere with study assessments
- Uncontrolled angina pectoris, cardiac failure or clinically significant arrhythmias

POPULATION (3)

EXCLUSION CRITERIA (2)

- Continuous use of immunosuppressive agents equivalent to >10 mg daily prednison
- Concurrent use of the antiviral agent sorivudine or chemically related analogues, such as brivudine
- Neurotoxicity > CTC grade 1
- Pregnancy or breast feeding
- Patients (M/F) with reproductive potential not implementing adequate contraceptive measures
- Gastric or gastro-oesophageal stent within radiation field

SCREENING FAILURE

- No informed consent/ informed consent but not eligible (screening file in ISF)
- Please report this to criticstrials@nki.nl

CHEMOTHERAPY: ARM 1 & ARM 2

DOC: DOCETAXEL, OXALIPLATIN, CAPECITABINE

- Capecitabine
  - Diary to enable adequate dose monitoring
  - Per cycle

RADIOTHERAPY (1) ARM 2 & ARM 3

QA RADIOTHERAPY

- CRITICS-I: quality of treatment delineation is important for outcomes
  - Treatment delineation is challenging

- Assurance quality treatment delineation
  - Prior treatment: planning audit
  - During trial

- Plannings audit: test treatment plan in all institutes at one CT+treatment delineation
  - PTV $D_{2\%}$
  - PTV $V_{95\%}$
  - Liver D_{mean}
  - Heart V_{40Gy}
  - Kidneys V_{18Gy}
  - Spinal cord D_{max}

- Treatment delineation atlas available (on website: www.criticstrials.nl)

RADIOTHERAPY (2) ARM 2 & ARM 3

PLAN QA: DURING TRIAL

- All treatment delineations of each subject have to be sent to the AVL prior start treatment
  - Add PDF: localisation, clinical stage (if known; size, lymph node status), gastroscopy report, conclusion of diagnostic CT scan
  - Or alternatively: send a secure email
- These will be judged and annotated by a radiation oncologist from the AVL via surfdrive
- <48h comments will be sent (PDF or RTstruct)
  - Please report if changes are accepted/rejected (criticstrials@nki.nl)
- Thereafter, planning will be started
- Treatment plan will be sent to the AVL in retrospect (plan report) rtstudieondersteuning@nki.nl

SURGERY

SURGERY PROTOCOL

- Staging laparoscopy: mandatory for all patients (before inclusion study), will be recorded in CRF
  - If laparoscopy is positive (macroscopic deposits or positive cytology); patient not eligible
  - Presence/absence of ascites, tumor deposits, ovarium metastasis, serosal tumor involvement. Number+localisation biopsies. Other relevant findings.
- (Sub)total gastrectomy + D2 lymph node dissection
- Surgical specimen: proper orientation and labelling, will be recorded in CRF
  - Specimen will be marked: proximal and distal ends, lesser and greater curvature
  - Specimen will be delivered as soon as possible to the department of pathology, preferably fresh tissue
  - Lymph nodes will be submitted in separate specimen pots (N1/N2)/ or will be clearly marked in the resection specimen
- Perioperative toxicities will be scored using the Clavien-Dindo classification (other toxicities will be scored using CTC AE 4.0)

PATHOLOGY

- TNM **8th** edition
- Biopsies
  - Lauren classification type (intestinal, diffuse, unclassifiable)
- Resection specimen
  - Response evaluation
  - Lymph nodes per station
  - CRF will be filled in by local pathologist
- Central pathology review
  - After postoperative MDO
  - Biopsies
  - Photographs
  - Resection specimen
- SOP for logistics

TRANSLATIONAL RESEARCH (1)

1. Relationship of histopathological parameters with primary tumour regression and clinical outcome
   - Central review of diagnostic biopsies and resection material by Dr. N.C.T. van Grieken (Vumc) and Prof. dr. H. Grabsch (UMC Maastricht)

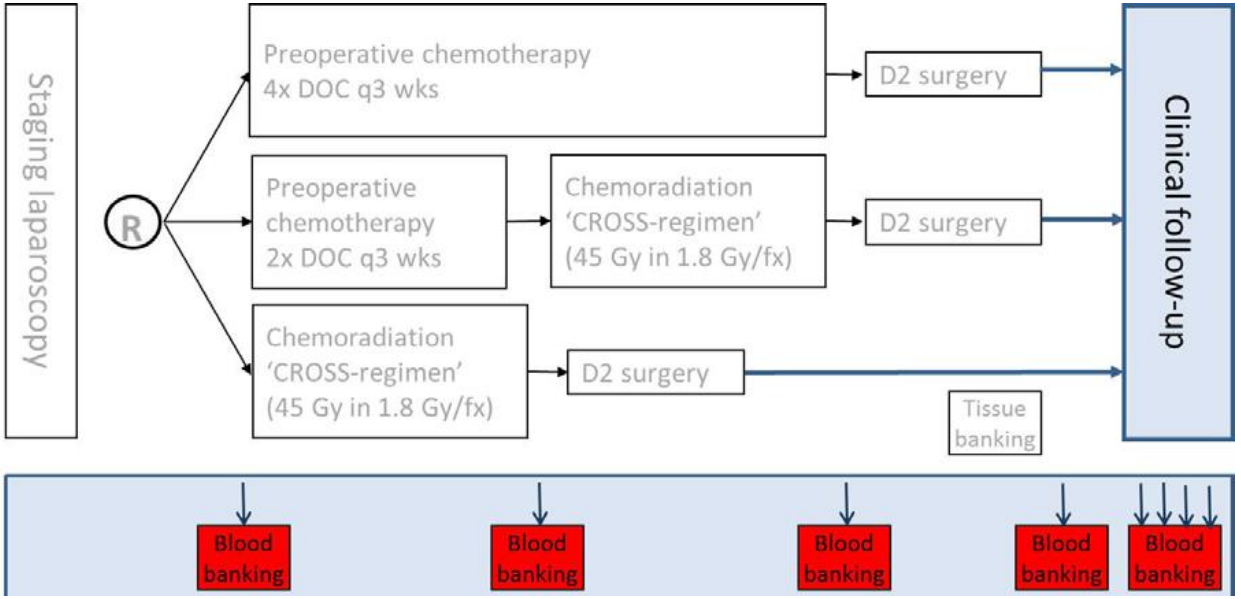
2. Relationship of genomic changes in the tumour with clinical outcome
   - Purpose: to find biomarkers that may predict clinical response to treatment
   - Several laboratory assays will be used to detect genomic changes

3. Relationship of cell free circulating tumour DNA (ctDNA) with clinical outcome **(participation is optional per patient)**

TRANSLATIONAL RESEARCH (2)

RELATIONSHIP CTDNA WITH CLINICAL OUTCOME (1)

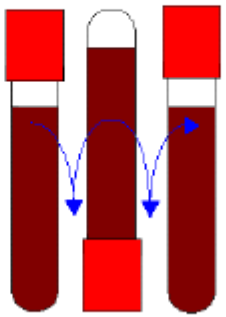
- Blood collection and shipment procedure
  - Patients can optionally participate in this part of the protocol
  - Signed informed consent specifically for this optional translational side of the study
  - Appointments necessary when treatment will be conducted in more than 1 centre



TRANSLATIONAL RESEARCH (3)

MODIFICATION COMPARED TO CRITICS-I

- Lab form available at web site (www.criticstrials.nl)

Blood collection in 10 ml tube (Streck)	Label tube: patient ID, date, date of birth	Gently invert tube 4-5 times	Send in provided shipping material
			

TRANSLATIONAL RESEARCH (5)

Naam ziekenhuis: .....

Patiënt randomisatie nummer: ⌊_ _ _⌋

Geboortejaar *: ⌊_ _ _ _⌋

Afname datum *: _ _ / _ _ / _ _ _ _ **Tijd ^:** _ _ hr _ _ min

* (dd/mm/jjjj) ^ (24 uur notatie)

Deze afname is (**ARM 1**):

- Vóór start behandeling ☐
- Na 4 kuren chemotherapie (DOC)(= preoperatief) ☐
- 1 maand postoperatief ☐
- Aantal maanden follow-up (3, 6, 9, 12, 18, 24) ☐ ____ maanden
- Recurrence ☐ ____ maanden na chirurgie

Afnameprotocol:

- De patiënt zit rustig op een stoel.
- Met een vacutainer Streck tube (meegeleverd met verpakkings- en verzendmateriaal) wordt er veneus bloed uit de elleboog afgenomen.
- Op de buizen wordt vermeld: CRITICS-II, patiënt randomisatie nummer en datum en tijd van afname
- De buizen worden direct met dit ingevulde formulier verstuurd in het meegeleverde verpakkingsmateriaal met antwoordnummer.

VERGEET NIET DE PATIENT RANDOMISATIE NUMMER EN AFNAMEDATUM OP DE BUIZEN TE VERMELDEN !!

HRQL/POCOP

HEALTH RELATED QUALITY OF LIFE (HRQL)

- Will be carried out based on the Prospective Observational Cohort study of Oesophagogastric cancer Patients (POCOP)
- A prospective nationwide study of the Dutch Upper GI Cancer Group (DUCG)
- Part of the CRITICS-II, **no** additional informed consent
- **Timeline HRQL:**
  - Baseline – pre-surgery
  - First year: every 3 months
  - Second year: every 6 months
  - After 2 years: yearly (until 5 years after surgery)
- Will be coordinated by the POCOP/profiles

- Important: inform POCOP about date of start treatment, date of surgery/evaluation CT and death

Treatment	Baseline ≤ 4 wks before randomisation	Randomisation	max 15 working days between randomisation and start of treatment	2 x DOC		CRT					interval 6-8 weeks	Surgery [4]	Follow up						
				DOC 1	DOC 2	CRT 1	CRT 2	CRT 3	CRT 4	CRT 5			Mth 1	Mth 3	Mth 6	wk 52 from R = ± mth 7,5	Mth 9	Mth 12	q6 mth until 5 yrs
History and physical																			
Medical History	X																		
Physical Examination /Vital signs	X			X	X	X	X	X	X	X		X	X	X	X		X	X	X
Weight/ Heigth/ WHO PS	X			X	X	X	X	X	X	X		X	X	X	X		X	X	X
ASA score												X							
Toxicity	X			X	X	X	X	X	X	X		X	X	X	X		X	X	X
Dietician	X																		
Laboratory																			
Hematology [6]	X			X	X	X	X	X	X	X		X	X	X	X		X	X	X
Creatinine [7]	X			X	X	X	X	X	X	X		X	X	X	X		X	X	X
Biochemistry [8]	X			X	X	X	X	X	X	X		X	X	X	X		X	X	X
Additional assessments																			
Esophagogastroduodenoscopy (EGD) [1]	X		X [11]																
Endoscopic Ultrasonography (optional) [10]	X																		
Staging laparoscopy	X																		
CT scan chest and abdomen	X											X				X [5]			
Renography [2]	X																		
PET-scan (optional per site)	X																		
HRQL																			
questionnaire (POCOP)			X									X		X	X		X	X	X [9]
Translational research																			
Plasma for ctDNA analysis (optional per patient) [3]			X		X					X			X	X	X		X	X	X [3]

1) consist of:
- representative tumour biopsy samples
- in case of malnutrition placement of feeding tube

2) if on CT abdomen or biochemically signs of impaired renal function

3) after each treatment modality and at recurrence; until 2 years after surgery

4) all assessments are pre-surgery

5) CT scan at 1 yr after randomisation (+/- 1 week)

6) Hb, WBC, Neutrophils, Platelets

7) Creatine and creatine clearance calculated according to Cockgraft Gault

8) Bilirubin, Alk. phosphatase, ASAT, ALAT, γGT, LDH, Albumin

9) POCOP questionnaires will be done 6 monthly in year 2 and yearly thereafter

10) Advocated if stage Ia disease (T1N0) is suspected

11) If applicable in the opinion of the treating physician

GCP GUIDELINES

LAW AND DECLARATION

- Declaration of Helsinki
- ICH/GCP guidelines

LAWS AND REGULATIONS

- EU Clinical Trial Directive
- **GDPR**/ AVG
- **WMO** / WGBO

BASIC PRINCIPLES GCP

- Protection of subjects
- Quality of data
  - DMP: What, why and how datamangement planning (EDC: audit trail)
  - Quality Assurance (monitoring)

GCP GUIDELINES

RESPONSIBILITIES PRINCIPAL INVESTIGATOR

- A sponsor/ PI can outsource **tasks**
  - not the responsibility for correct and timely execution of the study

- PI can delegate tasks to **qualified** personnel,
  - remains **responsible** for
    - Conducting the research
    - Intergrity, helath and well-being of subject
  - **delegated** tasks: delegation log

MONITORING

MONITOR PLAN

- Medium risk
- After 3 patients who had surgery
- 2-3 visits per site
- Follow up: depending on findings (2 out of 10/ 2 out of 15)

INDEPENDENT MONITOR (AVL)

- Informed consent
- In/ exclusion criteria
- Source Data Verification (critical data and Adverse Events ≥ grade 2)
- SAE/SUSAR
- Investigator Site File (del log)

DATA COLLECTION

ELECTRONIC CRF (ALEA)

- **RANDOMISATION**
  - Notification (local investigators, local data manager and …)

- **CRF**
  - Personal account (to be requested)
  - Pathology & Surgery CRF
  - Timelines for completion of data:
    - BL: 12 wk
    - Surgery: 8 wk
    - 1yr FU: 8 wk

- **SAE**
  - Paper
  - drugsafety@nki.nl (within 24hrs)
  - Clavien-Dindo → CTC AE v 4.0

SERIOUS ADVERSE EVENT FORM

A serious adverse event (SAE) has to be reported within 24 hours after occurrence of the SAE. A written report has to be sent to the Data Center (fax number: +31 (0) 20-512 2679). NKI-AVL, Trial Office, PO box 90203, 1006 BE Amsterdam, The Netherlands. In case of questions tel nr: +31 (0) 20-512 9047

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Protocol Number / Name	Patient study number	Patient birth year	Age	Report type: *(circle)*
M15CRI (CRITICS II)				1. Initial 2. Follow up 3. Final
Gender *m/f*	**Treating physician**	**Institution** *name/city*		

MAIN SAE, please indicate ONLY 1 with "X"	**Adverse event(s)**	**Onset date** *(dd/mm/yyyy)*	**Stop date** *(dd/mm/yyyy)*	**Severity** *(CTC)* 1= grade I/mild 2= grade II/ moderate 3= grade III/severe 4= grade IV/life threatening 5= grade V/death	**Relationship with treatment** 1= unrelated 2= unlikely 3= possible 4= probable **5= certain**							**Action taken regarding study drug** 1= none 2= dose reduced 3= delayed 4= interrupted 5= discontinued							**SAE outcome** 1= recovered 2= recovered with sequelae 3= improved 4= unchanged 5= worsened 6= fatal
					A*	B*	C*	D*	E*	F*	G*	A*	B*	C*	D*	E*	F*	G*	

***Please complete the study drug/treatment here**: A*=Docetaxel; B*= Oxaliplatin; C*= Capecitabine; D*= Paclitaxel; E*= Carboplatin; F*= Radiotherapy; G*= Surgery

Date AE became SERIOUS: *(dd/mm/yyyy)*		**End date of seriousness:** *(dd/mm/yyyy)*	

SAE category *(circle)*	**In case of death**	**Description of event** *(including date onset, diagnose, treatment for SAE)*
1. Death 2. Life threatening 3. Permanently disabling 4. Hospitalization/ Prolongation Date:…../……../…… 5. New cancer 6. Congenital anomaly 7. Overdose 8. Other ……	Date of death *(dd/mm/yyyy)* ……/……/…… Cause of death: ☐ 1. Malignant disease 2. Toxicity 3. Other, specify …… Autopsy performed: 0=No / 1=Yes ☐ *If yes, include report*	○ *description of event* ○ *delay/interruption treatment*

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SERIOUS ADVERSE EVENT FORM

Protocol Number / Name	Patient study number	Age	CCMO number
M15CRI (CRITICS II)			

Randomized treatment ARM:	Treatment week at time of SAE:			
☐ Arm 1: DOC + Surgery	DOC: ☐C1 ☐C2 ☐C3 ☐C4		☐ Surgery	☐ Follow Up
☐ Arm 2: DOC + CRT +Surgery	DOC: ☐C1 ☐C2	CRT: ☐W1 ☐W2 ☐W3 ☐W4 ☐W5	☐ Surgery	☐ Follow Up
☐ Arm 3: CRT + Surgery		CRT: ☐W1 ☐W2 ☐W3 ☐W4 ☐W5	☐ Surgery	☐ Follow Up

Trial drug(s) / Trial treatment	Start date first course *dd/mm/yyyy*	Most current treatment /administration dd/mm/yyyy	Dose *+ units*	Route *PO, IV, TOP, etc.*	Frequency
Docetaxel			mg	IV	
Oxaliplatin			mg	IV	
Capecitabine			mg	PO	
Paclitaxel			mg	IV	
Carboplatin			mg	IV	
Radiotherapy			Gy	Local	
Surgery				Local	
Number of last course given:	**Indication for use:**				

Relevant concomitant medications				Relevant tests			
Name	**Start date** *dd/mm/yyyy*	**Stop date** *dd/mm/yyyy*	**Daily dose** *+ units*	**Test**	**Date** *dd/mm/yyyy*	**Result** *value/units*	**Normal range** *value/units*

DUCG Dutch Upper GI Cancer Group

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REMARKS

SITE ACTIVATION

- **Board of directors**
  - Site specific PIF
  - RT QA (dummy run)
  - ALEA accounts
  - contract

- **CT scan** at 1 year after randomisation
  - Time point after surgery is different per arm
  - for exact time from randomisation see flowchart
  - Contact person will receive **reminder** appr 2 months prior to date

CONTACT AND WEBSITE

CONTACT

Principal Investigator	Marcel Verheij	m.verheij@nki.nl
Study Coordinator	Astrid Slagter	a.slagter@nki.nl
Project Manager	Pietje Muller	p.muller@nki.nl
General		criticstrials@nki.nl

DRUG SAFETY

SAE <24h	drugsafety@nki.nl

WEBSITE

www.criticstrials.nl