Summary Report

FOR

THE CLINICAL TRIAL

Preoperative combined radio-chemo-molecular targeted therapy (RC-MTTx) of primary locally advanced rectal carcinoma (cT3NxM0) – a phase II pilot study of preoperative treatment with Capecitabine (Xeloda), Bevacizumab (Avastin) and Radiotherapy (RTx)

EudraCT No.: 2007-006750-26

INVESTIGATIONAL MEDICINAL PRODUCT(S):	**Capecitabine (Xeloda®)** **Bevacizumab (Avastin®)**
INDICATION:	**Rectal cancer**
PHASE OF STUDY	**Clinical Phase II**
STUDY INITIATION DATE:	**19 March 2008**
STUDY COMPLETION DATE:	**27 February 2009**
SPONSOR:	**Austrian Breast & Colorectal Cancer Study Group**

Declaration: Above mentioned clinical Trial was conducted in compliance with Good Clinical Practices (including the archiving of essential documents), Declaration of Helsinki and regulatory requirements.

1 Overview

Title of Study:
Preoperative combined radio-chemo-molecular targeted therapy (RC-MTTx) of primary locally advanced rectal carcinoma (cT3NxM0) – a phase II pilot study of preoperative treatment with Capecitabine (Xeloda), Bevacizumab (Avastin) and Radiotherapy (RTx)

General remarks:
This two-stage study was terminated prematurely after a per-protocol safety evaluation of the phase 1 due to grade 3 toxicities in 50% of the enrolled patients.

Study Center(s): 11 Austrian sites of which 4 enrolled patients

Publications:
- Preoperative treatment with capecitabine, bevacizumab and radiotherapy for primary locally advanced rectal cancer – A two stage phase II clinical trial; Resch G, De Vries A, Öfner D, Eisterer W, Rabl H, Jagoditsch M, Gnant M, Thaler J, on behalf of the Austrian Breast and Colorectal Study Group; 2012 Radiotherapy and Oncology

Phase of Development: II

Studied Period (years): 19.03.2008 – 27.02.2009
- date of first enrolment: 04.07.2008 First Patient in
- date of last completed: 04.02.2009 Last Patient out

Subprotocol:
In the main study 1.5 Tesla-MRT (before and after neo-adjuvant therapy) was used for staging and therapy response. Within the substudy "Density measurement of tumor vascularity via 3-Tesla magnetic resonance tomography, during and after neoadjuvant radio-chemo molecular targeted therapy (RC-MTTx) in locally advanced rectal carcinoma within the ABCSG Study R04/TAKO 08" this shall be substituted by Dynamic Contrast Enhanced Magnetic Resonance Imaging (DEC-MRI) analysis and an additional examination three weeks after initiating neoadjuvant therapy in order to gain insights into micro vascularization of rectal tumors before, during and after radio-chemomolecular targeted therapy (RC-MTTx).

2 Objectives

The primary objective of the study was
- Feasibility and compatibility/safety of a preoperative therapy with Bevacizumab (Avastin) in combination with Capecitabine (Xeloda) and radiotherapy in patients with primary locally advanced rectal carcinoma (LARC)

The secondary objectives were:
- Assessment of response rate (downstaging of T-stage; pathological complete remission (pCR))

Objectives of the subprotocol:

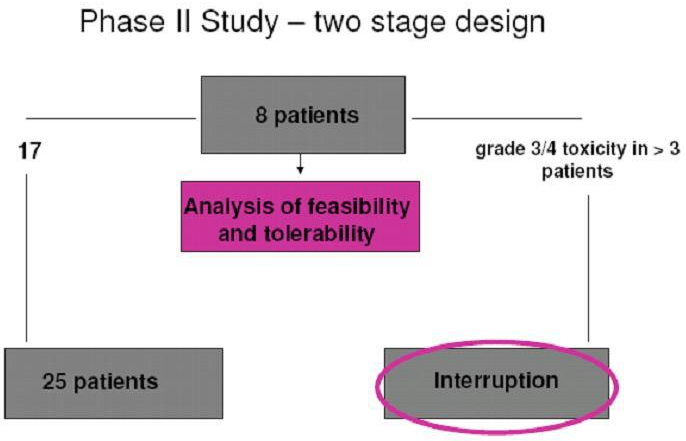
The primary objective of the subprotocol was:
- The systematic assessment and quantification of micro vascularization in LARC of the lower and middle third, without indication of distant metastases, using DEC-MRI before neoadjuvant RC-MTTx, 3 weeks after RC-MTTx, as well as 3 weeks after completion of neoadjuvant RCMTTx.

The secondary objective of the subprotocol was:
- Compare the respective individual changes during and after RC-MTTx with the level of tumor regression in the defined histopathological surgery sample.

3 Study Design

This single-arm multicenter phase II clinical trial evaluated the feasibility and safety of preoperative treatment with capecitabine, bevacizumab and RT in patients with LARC. Secondary endpoints included downstaging and pathologic response. A two-stage trial was designed with early termination at 8 patients if more than 3 patients experienced a common toxicity criteria grade 3 or 4 according to the NCI CTC guidelines (version 5.0) (Figure 1). Otherwise 25 patients were to be accrued.

Figure 1 2 stage trial design



4 Target Patient Population and Sample Size

Sample size calculation was based on the Two-Step-model of Simon (1989) for Grade 3 or 4 toxicities. The number of planned patients was 25 in total (8 for the first trial stage, additional 17 for the second trial stage). The number of actual analysed patients was 8 (only first trial stage).

5 Diagnosis and Main Criteria for Inclusion

Patients with primary, bioptically proven adenocarcinoma of the rectum in clinical stage cT3NxM0.

Inclusion criteria

1. age 18 – 80
2. no prior chemotherapy
3. no radiotherapy of the pelvis/abdomen and/or
4. tumor resection of rectal carcinoma
5. WHO condition grade 0-2
6. sufficient bone marrow resource
7. adequate hepatic and renal function
8. ability to take pills orally
9. exclusion of pregnancy
10. willingness to use proper contraception (if applicable)
11. life expectancy of at least 3 months
12. INR and aPTT ≤ 1.5 of low normal value
13. signed informed consent form prior to inclusion

Those main inclusion criteria were also applied in the subprotocol and subjects could be included in the subprotocol if they had already been included in the main protocol.

6 Study Treatment

Investigational Medical Product (IMP), dose and mode of administration

Chemotherapy
Capecitabine (Xeloda®) 825 mg/m² bid, on every radiation therapy day during the first 4 weeks RCTx

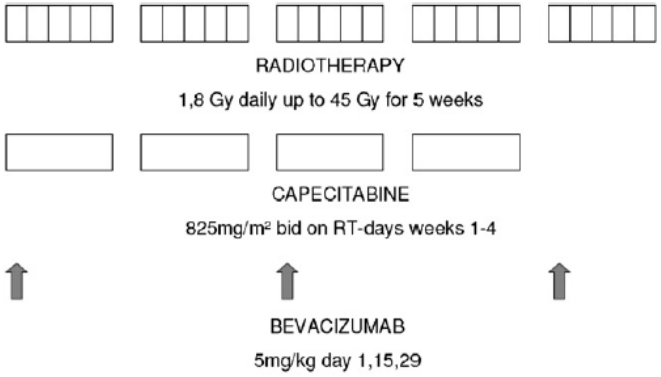
Molecular Targeted Therapy
Bevacizumab (Avastin®) 5 mg/kg KG; day 1, day 15, day 29

Duration of treatment

Combined radio-chemotherapy
Start of therapy within 28 days after bioptic diagnosis

Radiotherapy
5 x 5 days 1.8 Gy radiotherapy; total dosis of 45 Gy

Figure 2 Overview of the concomitant chemoradiation regimen



7 Examinations

Study duration per patient was max. 17 weeks:
- Start of therapy max. 28 days after diagnosis
- 5 weeks radio-chemotherapy
- min. 42 to max. 56 days break until surgery

Surgery was performed according to TME criteria and in compliance with a break of at least 42 and max. 56 days after the last administration of Bevacizumab.

For the subprotocol an additional examination three weeks after initiating neoadjuvant therapy before, during and after radio-chemomolecular targeted therapy (RC-MTTx) was performed.

8 Criteria of Evaluation

Efficacy:
- ypT0/1/2 tumor rate (= down-staging rate)
- pCR rate

Safety:
- SAE
- Laboratory values

9 Statistical Methods

All statistical calculations were solely descriptive.

10 Patient Disposition and Demography

In the first stage of this two-stage Phase II clinical trial, eight patients (4 women, 4 men) were enrolled. Median age was 70 years (range 55–76) and ECOG Performance Status (PS) 0/1 was 87.5%/12.5%. All patients had cT3 tumors and 5 patients (62.5%) had positive lymph nodes (LN) by imaging, 1 patient (12.5%) was LN-negative, 2 patients (25%) were not evaluable for N-stage. All patients received preoperative treatment. Surgery was done only in 7 patients, because in one patient peritoneal carcinomatosis was detected. Postoperative histology revealed grade 2 in 71.4% (5/7) and grade 3 in 28.6% (2/7).

11 Summary of efficacy results

Tumor downstaging was observed in 37.5% of patients with complete pathological response in two patients (25%).

12 Summary of safety results

Major side effects were mostly intestinal bleeding (grade 3, 25%), diarrhoea (grade 3, 25%), perianal and abdominal pain (grades 3 and 4, 25%) followed by haematological complications (anaemia: grade 3, 12.5%) and one postoperative intestinal obstruction (Table 1). There were no deaths related to preoperative radio immunochemotherapy or surgery.

Acute toxicities and perioperative complications grade 1-4 in patient 1-8; patient 3 and 6 had ypT0, patient 5 had ypT2.

Table 1 Adverse Events

Adverse event	Patient							
	1	2	3	4	5	6	7	8
Anemia	2		3					2
Thrombocytopenia	1		3			1		
Leukopenia	1	1	2			2		1
Neutropenia	1	1	1			1		1
Diarrhea			3	2		3		
Hand-food-syndrome	1	1						
Perianal bleeding	3		3					
Perianal pain	1		4					
Abdominal pain	3		3					
Nausea	1		1					
Dysuria		1	1					
Anastomotic dehiscence		2						
Postoperative ileus								3

13 Conclusion

After interim analysis of feasibility and tolerability, accrual was terminated according to protocol due to grade 3 toxicities in 50% of patients. Complete pathological response was seen in 25% of patients but was accompanied by considerable toxicity. Further clinical trials are needed to clarify the role of bevacizumab in this setting. Due to the early termination of the study no analysis of the subprotocol was performed.

14 References

Simon R. Optimal two-stage designs for phase II clinical trials. Controlled Clinical Trials 1989; 10:1-10