1. TITLE

A RANDOMIZED PHASE II OF BEVACIZUMAB, CAPECITABINE AND RADIATION THERAPY WITH OR WITHOUT OXALIPLATIN IN THE PREOPERATIVE TREATMENT OF LOCALLY ADVANCED RECTAL CANCER

AXE BEAM

EudraCT: 2007 – 007177 – 23
U.Z. Leuven Ref: S 51104
Other Internal Ref: ML5194
clinicaltrials.gov ID: NCT00828672

Final Study Report

ICH HARMONISED TRIPARTITE GUIDELINE
E3 CURRENT *STEP 4* VERSION
dated 30 November 1995

Important dates:
Initial approvals: Federal Agency for Medicines and Health Products 28-Sep-2008; lead Ethics Committee 12-Nov-2008
First patient enrolled: 22-Jun-2009
Last patient enrolled: 29-Sep-2013
End of recruitment notification: 30-Dec-2013
Last patient completed study treatment regimen: 03-Mar-2014
Database lock: 21-Apr-2016
End of trial notification: 23-May-2016
Last patient last visit (follow-up): expected Mar-2019

This study was performed in compliance with Good Clinical Practice

Sponsor: **University Hospitals Leuven**

Responsible: **Prof. Dr. Eric Van Cutsem**
University Hospitals Leuven
Digestive Oncology Unit
Address: Herestraat 49
B-3000 Leuven
Email: eric.vancutsem@uzleuven.be
Tel: +32 16 34 42 18
Fax: +32 16 34 44 19

Project supported by Roche and Sanofi

2. SYNOPSIS

Name of Sponsor/Company: **University Hospitals Leuven Digestive Oncology Unit** Academic trial – the sponsor is not the Market Authorization Holder of any of the drugs involved Unrestricted research grant by Roche Drugs delivered by Roche and Sanofi	Individual Study Table Referring to Part of the Dossier	*(For National Authority Use only)*
Name of Finished Products: **Avastin (bevacizumab) Roche** **Xeloda (capecitabine) Roche** **+/- Eloxatin (oxaliplatin) Sanofi**	Volume:	
Name of Active Ingredients: **Bevacizumab** **Capecitabine** **+/- Oxaliplatin**	Page:	

Title of Study: **A RANDOMIZED PHASE II OF BEVACIZUMAB, CAPECITABINE AND RADIATION THERAPY WITH OR WITHOUT OXALIPLATIN IN THE PREOPERATIVE TREATMENT OF LOCALLY ADVANCED RECTAL CANCER. AXE BEAM**

Study centres and Investigators:

01 UZ Leuven: Prof. Dr. Eric Van Cutsem – Prof. Dr. Karin Haustermans

02 Erasme Hospital Bruxelles: Prof. Dr. Jean-Luc Van Laethem – Prof. Dr. P Van Houtte

03 Cliniques Universitaires St. Luc Bruxelles: Prof. Dr. Yves Humblet - Prof. Dr. Pierre Scalliet

04 AZ St. Lucas Brugge: Dr. Joris Arts – Dr. Isabel Hutsebaut

05 AZ St Jan Brugge: Dr. Alain Bols – Dr. Geertrui Demeestere – no patients, closed out 27-Jan-2012

06 AZ Groeninge Kortrijk: Dr. Philippe Vergauwe – Dr. Karin Stellamans

07 CHU Sart-Tilman Liege: Dr. Marc Polus - Prof. Dr. Philippe Coucke

08 Augustinus Hospital Wilrijk: Dr. Reinhilde Weytjens – Dr Marika Rasschaert – no patients, closed out 24-Feb-2012

09 OLVZ Aalst: Dr. Luc Verbeke – Dr. Marc De Man

10 ZNA Middelheim Antwerp: Dr. Sabine Vanderkam – no patients.

11 H. Hart Ziekenhuis Roeselare: Dr. Jochen Decaestecker

12 Clinique Saint Elisabeth Namur: Dr. Jean-François Daisne – Dr. Jean-Charles Goeminne

13 Salvator St. Ursula Ziekenhuis Hasselt: Dr. Daan Walgraeve – Dr. Marc Brosens – approved by the Ethics Committee but not opened, no patients.

Publications (references):

Several abstracts were presented at international conferences and one full article on translational research was published. See Appendix 16.1.11 for complete set of references and available articles and abstracts.

Study period:	**Phase of development:** randomized, non-comparative, open-label phase II study
Date of first enrolment: 22-Jun-2009 Date of last completed treatment: 03-Mar-2014 Date of last completed follow up (FU) expected: Mar-2019	

Objectives:

General objectives:

This phase II trial assessed the activity of bevacizumab (AvastinTM) in combination with capecitabine (XelodaTM) and radiation therapy with or without oxaliplatin (EloxatinTM) in the pre-operative treatment of locally advanced rectal cancer, followed by TME resection, in a multicenter setting.

Endpoints:

Primary endpoint:

- Pathologic complete response (ypT0N0) rate

Secondary endpoints:

- Histopathologic R0 and negative CRM resection rate
- Pathologic down staging (ypT0-2N0) rate and Dworak Tumour Regression Grade (TRG)
- Clinical response rate at time of surgery (RECIST criteria based on MRI)
- Quality of mesorectal excision
- One month surgical complication rate
- Toxicity (CTCAE version 3.0)
- Loco-regional and distant recurrence/progression rates at 3 and 5 years
- Disease free survival and overall survival at 3 and 5 years

Methodology:

This randomized, non-comparative, open-label phase II study investigated a triplet (Arm A) and a doublet (Arm B) chemotherapy combination plus radiation in a neo-adjuvant setting for locally advanced rectal cancer.

After completion of all pre-treatment screening procedures, eligible patients were randomized in a ratio of 1:1 to one of the two treatment arms specified below. Patients received chemoradiotherapy until treatment completion or disease progression, unacceptable toxicity or patient refusal to continue. Patients were evaluated weekly or every two weeks by standard tests. Total mesorectal excision surgery was planned at 6-8 weeks after completion of chemoradiotherapy. Patients were considered off study 30 days after surgery. Recommendations for treatment adjustments in case of toxicity and use of certain concomitant medication were given in the protocol. Several blood samples and tumor biopsies were required for the translational component of the study.

All patient data were collected in an electronic CRF. Automated selected datasets were pre-built for extraction in the electronic platform. Raw data sets were extracted on 21-Apr-2016, formatted, worked and summarized in MS Excel 2010 and analysed using the SPSS v 24.0 statistical package.

Statistical methods:

Two-sided confidence intervals based on the exact binomial distribution were calculated at the 80% and 95% confidence level for the pathologic complete response (ypT0N0) rate, histopathologic complete resection rates (negative margins), pathologic down-staging (yp T0-2 N0) rate, TRG rate, clinical response rate at time of surgery, and one month complication rate.

Data on the quality of mesorectal excision were expected but not consistently collected. No analysis was possible on this secondary end-point.

Postoperative complications occurred between surgery and end of treatment visit (within 1 month post-surgery) and after the end of treatment in follow up are counted by treatment arm and are listed for each patient.

Toxicity is reported in a descriptive manner. Although frequency tables of the worst observed grade of toxicity were specified in the protocol, for the purpose of this report all events per patient were displayed. Worst grade per patient data is available upon request.

Estimates of the median disease-free survival and overall survival are/will be obtained using the Kaplan-Meier technique and described using medians and event-free rates at year 3 and 5. Confidence intervals for the medians will be calculated using the method of Brookmeyer and Crowley whereas the confidence intervals for the event-free rate will be obtained using the log-log transform and the Greenwood estimate of the standard deviation.

The loco-regional and distant recurrence/progression rates at 3 and 5 years are/will be estimated using cumulative incidences. For the analysis of local recurrence rates, as well as for the analysis of distant recurrences, only deaths not due to the disease are considered a competing risk.

The study was not powered to perform formal statistical comparisons of the treatment groups. Each treatment was described and presented separately.

Number of patients (planned and analysed):

80 patients planned (40 in each arm)

84 patients registered (43 in Arm A – triple combination and 41 in Arm B– double combination).

All 84 patients started treatment per protocol; all were considered eligible for and entered the safety analysis.

Efficacy analysis: one patient (04-011) was borderline eligible in terms of tumour position and MRI tumour characteristics [CRM at 4 mm; distance of tumour to anal verge > 5cm (6 based on colonoscopy report); see criteria below] which were considered to determine a slightly better prognostic compared to the other patients. Efficacy analysis was performed with and without this patient. Two patients with previous malignancies that were cured more than 5 years prior to study entries were considered eligible but entered in the deviation trackers. Other protocol deviations that occurred at screening – mostly blood and urine tests not done – were not considered influential on treatment effect and those patients were included in the efficacy analysis (intent to treat). Deviations are listed in Appendix 16.2.2.

Diagnosis and main criteria for inclusion:

Patients diagnosed with locally advanced rectal cancer (tumour beyond mesorectal fascia (T4) or tumour ≤ 2 mm from mesorectal fascia or T3 tumour < 5 cm from anal verge by MRI), histologically confirmed adenocarcinoma were considered eligible.

Other inclusion criteria were: age 18 years or older, body weight less than 120 kg, WHO performance status ≤2, adequate bone marrow, coagulation, hepatic and renal function, active contraception where applicable and ability to provide informed consent.

Patients with metastatic disease and previously treated with chemo- or radiotherapy for rectal cancer, as well as patients with clinical or social condition that would impede treatment were excluded.

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

Bevacizumab was provided by NV Roche SA. Bevacizumab is a recombinant humanized monoclonal antibody to VEGF (vascular endothelial growth factor).

Formulation: 400 ml vials

Route: IV

Dose, frequency & treatment mode: 5 mg/kg via a 1-hour IV infusion, on days 1, 15, 29 and 43, concurrently with radiotherapy. Bevacizumab administration precedes the oxaliplatin infusion in Arm A.

Capecitabine was provided by NV Roche SA. Capecitabine is an oral fluoropyrimidine carbamate in standard indication in this setting.

Formulation: film-coated 500 mg tablets

Route: oral

Dose, frequency & treatment mode: twice-daily 825 mg/m^2 (equivalent to a total daily dose of 1650 mg/m^2) days 15-47, 5 days per week, concurrently with radiotherapy.

Oxaliplatin was provided by Sanofi Aventis. Oxaliplatin is an alkylating agent consisting of platinum complexed to oxalate and diaminocyclohexane.

Formulation: 100 ml vials

Route: IV

Dose, frequency & treatment mode (In Arm A only): 50 mg/m^2 via a 1-hour IV infusion, on days 15, 22, 29, 36 and 43, concurrently with radiotherapy.

The total dose of radiotherapy was 45 Gy, with 1.8 Gy/day, administered days 15-47, 5 days per week. Radiotherapy started within 4 hours after bevacizumab infusion.

Surgery with curative intent (total mesorectal excision, TME) was planned to be performed within 6-8 weeks after the end of chemoradiation for all patients and was considered as part of the study protocol.

Investigational Arm A:

Oxaliplatin + Capecitabine + Bevacizumab + Radiotherapy followed by surgery (TME).

Investigational Arm B:

Capecitabine + Bevacizumab + Radiotherapy followed by surgery (TME).

Multiple batches of study labelled medication were used. Detailed information is enclosed in Appendix 16.1.6

Duration of treatment:

5+2 weeks chemoradiotherapy

6-8 weeks waiting time for surgery

Surgery

30 day mandatory safety follow up period

Total duration: 17-19 weeks

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

N/A

Criteria for evaluation:

Efficacy:

- Presence or absence of microscopic tumour within the surgical specimen, as verified by central pathology review. As per protocol, the investigational treatment Arm A was considered to be sufficiently active if ≥8 of 40 patients having started their allocated treatment on that arm have had pathologic complete response (≥ 20% ypT0N0 rate).
- Histopathologic negative CRM / R0 resection rate
- Pathologic response rates per arm (confidence intervals)
- Dworak tumour regression grade (TRG)
- Pathologic down-staging (ypT0-2 N0) rate
- Clinical response rate at time of surgery
- Quality of mesorectal excision – data were not consistently collected
- Disease status and survival in follow up at 3 and 5 years

Safety:

- One month post-surgery complication rate.
- All observed adverse events (rates per arm, duration, etc.)
- Serious adverse events
- Severe adverse events that did not meet the seriousness criteria
- Deaths
- Laboratory abnormalities (hematology and biochemistry)

Translational research:

Blood samples at 6 timepoints: flow cytometry to quantify numbers of endothelial progenitor cells and mature circulating endothelial cells. VEGF, bFGF and PIGF as angiogenesis factors and at PAI1 as tPA clotting factors.

Tumour tissue samples at 3 timepoints in consenting patients: immunohistochemistry and proteomic analysis up and downstream of the VEGF pathways (NFkB and MAPK pathways)

SUMMARY – CONCLUSIONS

EFFICACY RESULTS:

A high pathologic complete response rate (33% intent to treat and 34% central review set) was observed with the triplet schedule in Arm A (main endpoint reached). The pCR rate was 10% in ITT and 11% in centrally reviewed subgroup in Arm B. No difference between arms in terms of interval from stop of chemoradiotherapy and surgery occurred. Twenty patients had surgery at 9-12 weeks after stop of chemoradiotherapy, 10 in each arm. No significant differences between arms in terms of demographics, concomitant disease or other baseline characteristics that might influence response were noted.

Good tumour regression rates (Dworak 3-4) were of good magnitude (41% in Arm A and 24% in Arm B) in the centrally reviewed set, indicating the potential of these more aggressive regimens in selected populations with significant differences between the assessments of local pathologists and central reviewers.

All resected patients had proximal and distal resection margins free of tumour. Disease free survival and overall survival medians are not yet reached.

SAFETY RESULTS:

Overall, the study treatment was well tolerated although numerous mild events occurred. Treatment related toxicity was generally mild and manageable within reasonable intervals of time. Few dose reductions or cancellations were due to expected toxicity. The study was not powered to compare toxicity per arm. There were no deaths during study treatment; nine deaths occurred in post treatment follow-up period. None of the deaths were related to chemoradiotherapy involved by the protocol, most were due to disease progression. Thirty four serious adverse events occurred (22 in Arm A and 12 in Arm B), mostly postoperative.

The observed incidence of postoperative complications (wound infections, leaks, etc) was of 27% in an intent-to-treat analysis (23/84), slightly higher in Arm A (14/43=33%) than in Arm B (9/41=22%) with one fatality due to intra-operative tumour break and subsequent slow healing and severe infection at 12 weeks and one postoperative death due to lung embolism in a patient with a history of atrial fibrillation at 3 days. In the resected per protocol subset the incidence was 29%, with 34% in Arm A and 23% in Arm B. Twelve surgical re-interventions (one major pouch reconstruction), 6 in each arm were performed with good outcome. Except of the 2 postoperative deaths, all other patients recovered well. We have consulted with experienced surgeons within multidisciplinary team meetings and based on these consultations and advanced literature searches, we have concluded that the postoperative safety event rate was within acceptable limits for the type of surgery in this patient population.

There was no SUSAR; all SAEs were assessed as expected in this disease and treatment setting. No modifications to study protocol or patient information material were done due to toxicity during the study. No warnings or safety concerns due to the toxicity observed were raised nor sent to the Market Authorization Holders.

TRANSLATIONAL RESEARCH RESULTS:

A manuscript on translational research linked to the Axe Beam study has been published (1) and is provided in Appendix 16.1.11. Hypothesis generating molecular studies were performed, limited by the small sample size and possible interactions of effects due to multiple interventions. However, results suggested that PDGFA, PDGF-BB, CA-IX and pericyte-covered blood vessels may play a role as indicators of response to bevacizumab. Pericyte recruitment and vessel maturation indicated the susceptibility of the tumour vasculature to bevacizumab treatment in responders only.

CONCLUSION:

The addition of oxaliplatin to capecitabine and bevacizumab with radiotherapy seemed beneficial in terms of pathologic response rates in our patient population, with a slight increase in toxicity.

It is possible that the use of bevacizumab in combination with CRT increases the complete response rate with an increase of the incidence and severity of post-surgical complications.

Pathologic complete response rates reflect response to neo-adjuvant therapy but the value of pCR as a surrogate endpoint for disease free and overall survival is still to be established; based on current knowledge, long-term outcomes may be improved by the intensification of neoadjuvant or adjuvant therapy.

The risks and benefits observed on study remained consistent with the existing knowledge regarding the employed treatments and with our clinical experience in managing this patient population.

Patient selection criteria and timing of administration of multiple combinations are yet to be determined for maximal benefit for long term clinical outcomes.

PDGFA, PDGF-BB, CA-IX and pericyte-covered blood vessels may play a role as indicators of response to bevacizumab.

A full discussion on clinical and pathological findings will be published shortly.

Date of the report: 20-Feb-2017