Name of Sponsor: University Hospital Heidelberg represented in law by its Commercial Director Irmtraud Gürkan Im Neuenheimer Feld 672, 69120 Heidelberg, Germany
Name of Finished Product: Vectibix®
Name of Active Ingredient: Panitumumab
Title of Study: *identify version of protocol and amendments* Neoadjuvant radiochemotherapy combined with Panitumumab in locally advanced KRAS wild-type rectal cancer – NeoRec-1 Protocol Version/Date: Final 1.6 / 27. February 2012 For *Substantial amendments / interruptions or early termination* see below Early Termination at 16.08.12 due to very slow accrual
Study centre(s) and Principle Investigator(s): National Center for Tumor Diseases (NCT): University Hospital Heidelberg, Medical Oncology, Im Neuenheimer Feld 460, 69120 Heidelberg; Prof. Dr. med. Dirk Jäger (Coordinating Investigator) / University Hospital Heidelberg, Radiooncology und Radiation Therapy, Im Neuenheimer Feld 400, 69120 Heidelberg; Dr. Karin Potthoff (Principal Investigator) Krankenhaus Nordwest: Radioonkologische Klinik, Steinbacher Hohl 2-26, 60488 Frankfurt
Publication (reference): Not applicable

Studied period (years): *incl. interruptions, early terminations and discontinuations*	*Phase of development:*
date of first patient enrolment: 11.10.2011 date of last patient enrolment: 22.12.2011 date of last patient completed:30.04.2012	Phase 2

Objectives: Primary objective(s): To evaluate the anti-tumor efficacy of Panitumumab with combined radiochemotherapy with respect to the pCR (histopathological complete remission) rate. Secondary objective(s): Include objective response, pathological efficacy parameter, metabolic parameter, safety parameter and quality of life.

Methodology:

Open-label, single arm, multicenter, national, phase II trial

The purpose of this clinical trial was to determine whether the trial treatment has sufficient anti-tumour activity. The main analysis was a hypothesis test following the Simon's minimax two-stage design [Simon 1989]. A pCR rate of 30% was considered to qualify the study treatment as very promising for additional testing. Following this design one interim analysis of efficacy has to be performed at the end of the first stage. After accrual of 23 patients, recruitment has to be interrupted, if necessary, until a decision according to the first stage of Simon's design has been reached. The objective of the interim analysis was to allow the early stopping of the trial in case of an insufficient number of responders (pCR≤3). Otherwise additional 25 patients were to be enrolled and treated at the stage two. The treatment had to be rejected if no more than 11 pCR have been observed up to the end of stage two. The total sample size implied by this design is less or equal to 48.

Number of patients (planned and analysed):

- Patients planned:
  It was planned to include a total of 48 patients in two stages. During stage 1, 23 patients were to be enrolled and treated. The trial has to be continued to stage 2, with an additional 25 patients, if the observed number of responses (histopathological complete remissions) were > 3. Recruitment and treatment of patients has to be performed in 3 trial centers.
- Patients analysed: four.
  The study was stopped prematurely on 16.08.2012 after the inclusion of four patients

Diagnosis and main criteria for inclusion:

- Diagnosis: Locally advanced KRAS wild-type rectal cancer (ICD C20).
- Main inclusion criteria:
  Histologically confirmed, potentially resectable rectal adenocarcinoma staged as uT3/4, N0/1 by endosonography or cT3/4 by MRI of the pelvis with or without local lymph node metastases, but without evidence of distant metastases.

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

- Test product: Panitumumab intravenous, 6 mg/kg of body weight q2w d1-d57, (5 times total); begin on day 1 (run-in-phase) and subsequent application on days 15, 29, 43, and 57.
- Accompanied standard therapy: Radiochemotherapy has to be started on day 15 and consist of a percutaneous radiotherapy with an overall dosage of 50.4 Gy delivered in 28 fractions of 1.8 Gy, five times weekly, combined with 5-FU as a continuous infusion in a dosage of 300 mg/m2 per day on days 1-5 of every week over approximately 6 weeks

Duration of treatment:

Date of 1st administration: 24.10.11

Date of last administration: 27.02.12

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

Not applicable

Criteria for evaluation:

Primary endpoint(s):

The primary endpoint was the histopathological complete response rate (pCR) determined by means of the resection specimens.

Secondary endpoint(s):

- Objective tumor response rates assessed at day 14 by MRI of the pelvis and metabolic tumor response rates assessed by means of changes in the standardized uptake values (SUV) using FDG-PET-CT. Before surgery (week 12).
- Tumor response rates reassessed by MRI of the pelvis and FDG-PET-CT to determine objective response according to the revised Response Evaluation Criteria in Solid Tumors (RECIST).
- The rate of R0 and sphincter preserved resections.
- Safety evaluations including AEs, SAEs, standard laboratory assessments, and post-surgical complications from baseline through 30 days after surgery.
- Quality of life (QoL), assessed using the EORTC QLQ-C30 in combination with the colorectal cancer-specific quality of life questionnaire module (QLQ-CR29).
- Clinical outcome measures including distant metastases-free survival, relapse-free survival and overall survival after end of study and were assessed during routine follow up visits.

Statistical methods:

Due to the early termination of the study, only a descriptive analysis (tabulations and listings of the basic patient characteristics, and safety data) is performed.

SUMMARY - CONCLUSIONS

The database consisted of four patients. All four patients received study drug and are included in the final analysis. One patient discontinued prematurely due to lost to follow up. The primary diagnosis was adenocarcinoma in all four patients.

EFFICACY RESULTS:

Not applicable

SAFETY RESULTS:

The safety evaluation is based on all four patients. Adverse Events (AEs) were analyzed as TESS (treatment-emergent signs and symptoms). In total 40 AEs occurred in the four patients. 22 (55%) of the 40 AEs were judged to be definitely treatment-related. The most frequent AEs were dermatitis acneiform 7 (17.5%), diarrhoea 6 (15%), and radiation dermatitis 5 (12.5%). In total two AEs were considered to be serious in one patient of whom one AE (femal rectal-vaginal fistula, grade 3) the causality was reported as “probably” treatment related and one (radiogenic dermatitis, grade 3) was unrelated to the study drug. None of the four patients discontinued due to adverse events.

CONCLUSION:

The NEOREC-1 study was conducted to primarily assess the antitoumor activity of neoadjuvant radiochemotherapy combined with Panitumumab in locally advanced KRAS wild-type rectal cancer. Overall only four patients could be included into the study. Considering the premature close of this study any evaluation of efficacy and safety results are deemed inappropriate. The decision to stop this trial was not the result of a planned interim analysis or an accumulation of SAEs or deaths.

Substantial amendments / interruptions or early termination:	
Initial Protocol:	Version/Date: 1.4 / 31. January 2011, CA approved 24.03.2011
Substantial Amendments:	IB 9.2, CA approved 26.05.2011
	Protocol 1.5 / 10. August 2011, CA approved 05.09.2011: Adjustment of biopsy sampling and preparation.
	IB 10, CA approved 31.03.2012
	Protocol 1.6 / 27. February 2012, CA approved 23.04.2012: Adaption of contact details, study timelines, screening period and time schedule of measures at trial visits
Interruption of trial:	none
Early termination of trial:	16.08.2012 due to the very slow accrual
Date of the report:	
19.12.2012	