NCT NATIONALES CENTRUM FÜR TUMORERKRANKUNGEN HEIDELBERG

getragen von:
Deutsches Krebsforschungszentrum
Universitätsklinikum Heidelberg
Thoraxklinik-Heidelberg
Deutsche Krebshilfe

Ergebnisbericht nach §42b Arzneimittelgesetz (AMG)

Name of Sponsor/Company:

University of Heidelberg
represented in law by its Commercial Director Irmtraut Gürkan

Im Neuenheimer Feld 672
69120 Heidelberg
Germany

Name of Finished Product:

Cis-GRY® 10 mg/10 ml, 50 mg/50 ml, 100 mg/100 ml (TEVA GmbH) [1)]

FLUOROURACIL-GRY, 50 MG/ML (TEVA GmbH) [2)]

IntronA® 18 Mio I.E./3 ml, -25 Mio I.E./2,5 ml (SP Europe essex pharma) [3)]

Name of Active Ingredient:

[1)] Cisplatin

[2)] Fluorouracil

[3)] Interferon alpha-2b

Title of Study:
identify version of protocol and amendments

A Randomized Multicentre Phase II Trial Comparing Adjuvant Therapy in Patients with Resected Pancreatic Adenocarcinoma Treated With Interferon Alpha-2b and 5-FU Alone or in Combination with Either External Radiation Treatment and Cisplatin (CapRI) or Radiation alone regarding Event-Free Survival – CapRI-2.

Protocol Version 2.0 of 08/02/2008:
Initial submission

Protocol Version 2.1 of 24/06/2008:
Amendment 01, concerning radiation treatment and radiation field configuration.

Protocol Version 2.2 of 04/08/2008:
Amendment 02, Description of exclusion criteria in more detail for: heart disease, lung disease and ECOG status. Serious uncontrolled acute infections and any contra-indications for any investigational product were added as exclusion criteria. Occurance of mental diseases were added as individual criteria for trial termination. Toxicity-based dose adjustments were concretized.

Protocol Version 2.3 of 11/08/2008 and Protocol Version 2.4 of 29/09/2008:
Amendments 03/04 defined the term “tumor recurrence” within the definition of objectives more clearly. Expected trial duration was prolonged. Typos and contact details were corrected.

Study centre(s) and Principle Investigator(s):

University Hospital Heidelberg
National Center for Tumor Diseases (NCT) Heidelberg
Department of Surgery
Prof. Dr. Angela Märten (Initial Coordinating Investigator till 19. Apr. 2009)
Prof. Dr. Moritz Wente (Coordinating Investigator from 20. Apr. 2009 till 15. Nov. 2009)
Prof. Dr. Jan Schmidt (Coordinating Investigator from 16. Nov. 2009)
Im Neuenheimer Feld 460
69120 Heidelberg

Universitätsklinikum Greifswald
Klinik für Innere Medizin A
Prof. Dr. Markus Lerch (Principle Investigator)
Friedrich-Loeffler-Str. 23a
17475 Greifswald

Universitätsklinikum Ulm
Klinik für Innere Medizin I
Prof. Dr. Götz von Wichert(Principle Investigator)
Albert-Einstein-Allee 23
89081 Ulm

Medizinische Hochschule Hannover
Klinik für Gastroenterologie / Hepatologie / Endokrinologie
Prof. Dr. Arndt Vogel (Principle Investigator)
Carl-Neuberg-Straße 1
30625 Hannover

Publication (reference):

Study protocol: A Randomized Multicentre Phase II Trial Comparing Adjuvant Therapy in Patients with Interferon Alpha-2b and 5-FU Alone or in Combination with Either External Radiation Treatment and Cisplatin (CapRI) or Radiation alone regarding Event-Free Survival – CapRI-2; *Angela Märten, Jan Schmidt, Jennifer Ose, Sabine Harig, Ulrich Abel, Marc W Münter, Dirk Jäger, Helmut Friess, Julia Mayerle, Guido Adler, Thomas Seufferlein, Thomas Gress, Roland Schmid and Markus W Büchler;* BMC Cancer 2009, 9:160
doi: 10.1186/1471-2407-9-160

Studied period (years):
incl. interruptions, early terminations and discontinuations

4. Nov. 2008 (First patient in)

2.Feb. 2010 (Last patient in)

15. May 2010 early termination of trial

Phase of development:

Not applicable

Objectives:

Primary objective was the comparison of the treatment groups with respect to event-free survival. An event was defined as tumor recurrence, grade 3 or grade 4 toxicity (according to CTC 3.0), or death (whichever occurs first).
Secondary objectives were comparison of the treatment groups with respect to safety, OS, RFS, QoL.
Immunomonitoring to screen for predictive markers and to analyze the mode of action of IFN-alpha was to be performed as accompanying translational research.

Methodology:

Controlled, open, prospective, randomized, multi-center clinical phase II trial with three parallel arms comparing the CapRI regimen with two de-escalations of this regimen.

Sample size calculations were based on the three-group comparison (differences in the three 6-month event-free rates r1,r2,r3 corresponding to CapRI (Arm A), CapRI light (Arm B), and CapRI ultra light (Arm C), respectively) and carried out by means of computer simulations using the following main assumptions: Equal group sizes, failure times arising from an exponential distribution, individual follow-up duration of ≥6 months, duration of patient enrolment 6,12, or 18 months, For r1=2%, r2=10%, r3=15% the minimal sample size leading to an estimated power of ≥80% was 37 per group. Similarly, for r1=2%, r2=5%, r3=15% the necessary sample size estimated by the simulations was 38 per group. To accommodate a maximum drop-out rate of 15% the total sample size was increased to 135.

Number of patients (planned and analyzed):

Planned No.: 135

Analyzed No.: 19

Diagnosis and main criteria for inclusion:

Patients with Resected Pancreatic Adenocarcinoma.

Inclusion criteria (Protocol Version 2.4, in brief):

- Patients after R0/R1 resection of pancreatic ductal adenocarcinoma
- No evidence of metastasis
- Adequate lab parameters (bone marrow-, liver and kidney function)
- Therapy start within eight weeks after surgery

Exclusion criteria (Protocol Version 2.4, in brief):

- Patients with known severe depression
- Patients with severe heart diseases (NYHA stage three and four) or severe lung disease (COPD Grade III, asthma Grade IV)
- General condition worse than ECOG 2
- Previous radiotherapy in respective region
- Previous chemotherapy for pancreatic carcinoma
- Mental diseases ICD-10-code F30, F31, F32.2 ff. or F33.2 ff.
- Pregnancy or breastfeeding
- Serious uncontrolled acute infections at the time of therapy initiation

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

- Arm A: Cisplatin, 5-Fluorouracil, INTRON A® and external beam radiation (CapRI)
- Arm B: 5-Fluorouracil, INTRON A® and external beam radiation (CapRI light)
- Arm C: 5-Fluorouracil and INTRON A® (CapRI ultra light)

5-FU - 200mg/m^2/day by continuous intravenous infusion for three cycles at days 1-38, 64-101, and 120-161.

Interferon alpha-2b - 3 million units SQ MWF three times weekly during days 1-38 (17 total doses) plus one injection prior to treatment start (LDI) given during week -1 (approx. day -6). Interferon alpha-2b (Intron A) was to be administered subcutaneously in the thigh, outer surface of the upper arm, or lower abdomen outside the radiation field.

Cisplatin (arm A) - 30 mg/m^2 (capped at BSA = 2m^2; maximum single cisplatin dose of 60 mg) IV on days 1, 8, 15, 22, 29, 36 (6 doses).

Radiotherapy (arm A and B): The pancreatic bed covered with a total dose of 50.4 Gy in 28

fractions over 5.5 weeks (1.8 Gy/day).

Batch No.: Not applicable

Duration of treatment:

In all arms, patients were treated for 23 weeks. Details see above.

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

Not applicable; all trial arms were experimental.

Criteria for evaluation:

Efficacy:

The planned analysis of the primary and secondary efficacy variables was as follows: Kaplan-Meier product-limit estimates for the "survivor functions" (see below) of EFS, OS, and RFS, 95%-confidence intervals for the EFS, OS and RFS rates at 6 months using Greenwood's formula. Differences between the study groups with respect to event-free survival will be tested using a closed testing procedure, starting with a three-group comparison, followed by three pairwise comparisons, each on the nominal a=5% level. For each comparison the logrank test will be used.

Primary endpoint:

Event-free survival (EFS); defined as time from resection to objective tumor recurrence, grade 3 or grade 4 toxicity (according to CTC 3.0), or death (whichever occurs first), and censored by the end of observation.

Secondary endpoints:

a) Overall survival (OS), defined alternatively as time from randomization to death or time from resection to death.
b) Recurrence-free survival (RFS) defined alternatively as time from randomization to death/recurrence (whichever occurred first) or time from resection to recurrence/death (whichever occurs first).
c) QoL: QLQ-C30 and Pan-26
d) Immunological parameters: VEGF, bFGF, Il-2, IFN-alpha, TNF-alpha, IL-12, sMIC, iC3b.

Safety:

The planned assessment of safety was mainly based on the frequency of adverse events and on the number of laboratory values falling outside of pre-determined ranges and/or showing a distinct worsening from baseline.

The following parameters were obtained according to the schedule of assessments:

Physical Examination

- Complete clinical evaluation of all body systems
- Vital Signs
- Measurement of blood pressure, heart rate, body temperature and weight.

The following laboratory samples were obtained in accordance with the schedule of assessments:

- Haematology: leukocytes with differential count, haemoglobin, thrombocytes
- Chemistry: SGOT/AST, SGPT/ALT, total bilirubin, potassium, calcium, magnesium, serum creatinine, glucose
- Pregnancy test
- Tumor marker: CA 19-9
- Coagulation Parameters: INR

The patients were asked whether any adverse event had occurred since the last visit.

Statistical methods:

The CapRI-2 trial was stopped prematurely after the inclusion of merely 19 patients. Under these circumstances, any confirmatory statistical analysis was deemed inappropriate. Summary descriptive statistics were confined to basic patient characteristics as well as adverse events.

SUMMARY - CONCLUSIONS

EFFICACY RESULTS:

Not applicable

SAFETY RESULTS:

Tables of adverse events were produced. Only descriptive statistical analyses were done. The trial was stopped prematurely. The decision to stop this trial was not the result of a planned interim analysis or an accumulation of SAEs or deaths in this trial; no SAEs or deaths occurred during the conduct of this trial.

CONCLUSION:

Not applicable

Substantial amendments / interruptions or early termination:

See above: "*Title of Study*"

The CapRI-2 trial was terminated early for reasons of an unfavorable change of its risk-benefit-balance arising from new results from the CapRI pre-trial: No significant differences of survival between its two trial arms were found whereas the investigational CapRI-scheme showed higher toxicities compared to the standard 5FU/FA-Scheme.

Date of the report:

23. May 2012