KURZPROTOKOLL
RAINFALL

Öffentlicher Titel	Phase III Studie zu Capecitabine/Cisplatin mit oder ohne Ramucirumab beim Adenokarzinom des Magens oder gastroösophagealen Übergangs
Wissenschaftl. Titel	A Randomized, Double-Blind, Placebo-Controlled Phase 3 Study of Capecitabine and Cisplatin With or Without Ramucirumab as First-line Therapy in Patientes With Metastatic Gastric or Gastroesophageal Junction Adenocarcinoma (RAINFALL)
Kurztitel	RAINFALL
Studienart	multizentrisch, prospektiv, randomisiert, doppelblind, zweiarmig
Studienphase	Phase III
Erkrankung	Verdauung: Magen-/Speiseröhrenkrebs (Magen-/Ösophaguskarzinom): Erstlinie
Ziele	- The primary objective of this study is to compare PFS of ramucirumab in combination with capecitabine (or 5-fluorouracil [5-FU]) and cisplatin versus placebo in combination with capecitabine (or 5-FU) and cisplatin as first-line treatment in patients with metastatic gastric or gastroesophageal junction (GEJ) adenocarcinoma. - a. to compare the overall survival (OS) between treatment arms - b. to compare the time to progression (TTP) between treatment arms - c. to compare the objective response rate (ORR) between treatment arms - d. to compare the disease control rate (DCR) between treatment arms - e. to compare the duration of response (DOR) between treatment arms - f. to evaluate the safety profile of ramucirumab in combination with capecitabine (or 5 -FU) and cisplatin - g. to compare the quality of life and health status between treatment arms - h. to compare time to deterioration in Eastern Cooperative Oncology Group (ECOG) performance status (PS) between treatment arms - i. to assess the pharmacokinetics (PK) of ramucirumab
Einschlusskriterien	- Have a histopathologically confirmed diagnosis of metastatic gastric or gastroesophageal junction (GEJ) adenocarcinoma. All histologies of nonsquamous cell origin including undifferentiated carcinoma can be considered. - Have not received any prior first-line systemic therapy (prior adjuvant or neoadjuvant therapy is permitted). Patients whose disease has progressed after >12 months following the last dose of systemic treatment for adjuvant/neoadjuvant disease can be considered. - Have measurable or nonmeasurable but evaluable disease determined using guidelines in Response Evaluation Criteria In Solid Tumors, Version 1.1 (RECIST v.1.1). Baseline tumor assessment should be performed using a high resolution CT scan using I.V. and oral contrast unless clinically contra-indicated. MRI is acceptable if a CT cannot be performed. - Have a performance status of 0 or 1 on the Eastern Cooperative Oncology Group scale (ECOG PS) at baseline (see Attachment 5). - Have adequate organ function, as determined by: - a. Hepatic: Total bilirubin 1.5 times upper limit of institutional normal value (ULN), aspartate transaminase (AST) and alanine transaminase (ALT) 3 x ULN for ALT/AST if no liver metastases, < 5 x ULN if liver metastases. The albumin level must be higher than 2.5 g/dl (or equivalent) measured in a non-dehydrated state. - b. Renal: Calculated creatinine clearance must be 60 mL/min using the Cockcroft-Gault formula (see Attachment 6) or equivalent method. Methods using radiolabeled markers (for example, 51-CrEDTA or Tc99m-DTPA) to measure glomerular filtration rate [GFR] are also acceptable. The patient’s urinary protein is < 2+ on dipstick or routine urinalysis. If urine dipstick or routine analysis indicates proteinuria 2+, then a 24-hour urine must be collected and must demonstrate < 2g of protein in 24 hours to allow participation in the study.

- c. Hematologic: Absolute neutrophil count (ANC) 1.5 x 109/L, hemoglobin 9 g/dL (5.58 mmol/L; packed red blood cell transfusions are not allowed within one week prior to baseline hematology profile), and platelets 100 x 109/L.
- d. Coagulation: The patient must have adequate coagulation function as defined by International Normalized Ratio (INR) 1.5 and a partial thromboplastin time (PTT) 5 seconds above the ULN (unless receiving anticoagulation therapy). Patients receiving warfarin should be switched to prophylactic doses of low molecular weight heparin and have achieved stable coagulation profile prior to randomization, unless clinically contraindicated. If patients continue to receive warfarin, the INR levels must be monitored and maintained at < 1.5 as per local practices. Consideration should be given to potential drug interactions (for example, CYP2C9 substrates) and an increased vigilance with respect to the monitoring of the patient's INR according to the investigator's judgment as clinically indicated.
- Are at least 18 years of age (or of an acceptable age according to local regulations, whichever is older).
- Have provided signed informed consent prior to any study specific procedures and is amenable to compliance with protocol schedules and testing.
- Have an estimated life expectancy of 12 weeks in the judgment of the investigator.
- Resolution to Grade 1 by the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE), Version 4.0, of all clinically significant toxic effects of previous anticancer therapies. Patients with non-serious and non-life-threatening toxicities, such as alopecia, altered taste or nail changes, can be considered.
- Eligible patients of reproductive potential (both sexes) must agree to use adequate contraception methods (hormonal or barrier methods) during the study period and at least 12 weeks after the last dose of study treatment or longer if required per local regulations.
- a. A highly effective method of birth control is defined as one that results in a low failure rate (that is, <1% per year) when used consistently and correctly, such as implants, injectables, combined oral contraceptives, some intrauterine contraceptive devices (IUDs), sexual abstinence, or a vasectomized partner. For patients using a hormonal contraceptive method, information regarding the product under evaluation and its potential effeca. A highly effective method of birth control is defined as one that results in a low failure rate (that is, <1% per year) when used consistently and correctly, such as implants, injectables, combined oral contraceptives, some intrauterine contraceptive devices (IUDs), sexual abstinence, or a vasectomized partner. For patients using a hormonal contraceptive method, information regarding the product under evaluation and its potential effect on the contraceptive should be addressed.t on the contraceptive should be addressed.
- b. Men who are sterile (including vasectomy) or who agree to use a reliable method of birth control and agree to use a reliable method of birth control and agree to not donate sperm during the study for at least 12 weeks following the last dose of ramucirumab or country requirements, whichever is longer, are eligible.
- c. Women who agree to use a reliable method of birth control, or are not of child-bearing potential due to surgical sterilization (at least 6 weeks following surgical bilateral oophorectomy with or without hysterectomy or tubal ligation) confirmed by medical history or due to menopause, are eligible. A "menopausal woman" is a woman with spontaneous amenorrhea for at least 12 months, not induced by a medical condition such as anorexia nervosa and not taking medications during the amenorrhea that induced the amenorrhea (for example, oral contraceptives, hormones, gonadotropin releasing hormone, antiestrogens, selective estrogen receptor modulators [SERMs], or chemotherapy).

- Have baseline clinical and laboratory parameters that are consistent with the requirements prescribed in respective labels and are suitable for consideration of treatment with capecitabine (or 5-FU) and cisplatin (for example, dihydropyrimidine dehydrogenase deficiency).
- Are willing to provide blood and tissue samples for research purposes. Submission of blood and tumor specimens is mandatory for participation in this study, unless restricted per local regulations.

Ausschlusskriterien

- Patients with adenocarcinoma of the esophagus are excluded.
- Patients with HER2-positive status as determined per local standards. Patients with a negative test or having an indeterminate result due to any reason can be considered, provided these patients are not eligible for treatment directed against tumors which overexpress HER2.
- Patients receiving chronic therapy with nonsteroidal anti-inflammatory agents (NSAIDs, for example, indomethacin, ibuprofen, naproxen, or similar agents) or other anti-platelet agents (for example, clopidogrel, ticlopidine, dipyridamole, or anagrelide) within 7 days prior to first dose of study treatment. Aspirin use at doses up to 325 mg/day is permitted.
- Have radiation therapy within 14 days prior to randomization. Palliative radiotherapy during the study, if clinically indicated, can be considered after consultation with the Lilly clinical research physician (CRP). Any lesion requiring palliative radiation or which has been previously irradiated cannot be considered for response assessment.
- Have documented brain metastases, leptomeningeal disease or uncontrolled spinal cord compression.
- Have significant bleeding disorders, vasculitis, or had a significant bleeding episode from the gastrointestinal tract within 12 weeks prior to randomization.
- Have experienced any arterial thromboembolic event, including myocardial infarction, unstable angina, cerebrovascular accident, or transient ischemic attack, within 6 months prior to randomization.
- Have symptomatic congestive heart failure (New York Heart Association II-IV) or symptomatic or poorly controlled cardiac arrhythmia.
- Have uncontrolled hypertension prior to initiating study treatment, despite antihypertensive intervention.
- Have undergone major surgery within 28 days prior to randomization, or central venous access device placement within 7 days prior to first dose of study treatment, except if the procedure is minimally invasive (for example, introduction of peripherally inserted central catheter [PICC] line) and the investigator does not anticipate any significant bleeding.
- Have a history of gastrointestinal perforation and/or fistulae within 6 months prior to randomization.
- Have a history of inflammatory bowel disease or Crohn’s disease requiring medical intervention (immunomodulatory or immunosuppressive medications or surgery) 12 months prior to randomization.
- Have an acute or subacute bowel obstruction or history of chronic diarrhea which is considered clinically significant in the opinion of the investigator.
- The patient has: o cirrhosis at a level of Child-Pugh B (or worse) or o cirrhosis (any degree) and a history of hepatic encephalopathy or clinically meaningful ascites resulting from cirrhosis. Clinically meaningful ascites is defined as ascites resulting from cirrhosis and requiring ongoing treatment with diuretics and/or paracentesis.
- Have known allergy or hypersensitivity to any components of study treatment.

- Are currently enrolled in, or discontinued study drug within the last 28 days from a clinical trial involving an investigational product or non-approved use of a drug or device (other than the study drug used in this study), or concurrently enrolled in any other type of medical research judged not to be scientifically or medically compatible with this study. Patients participating in surveys or observational studies are eligible to participate in this study.
- Severely immunocompromised patients (other than that related to the use of corticosteroids) including patients known to be HIV positive.
- Are pregnant or lactating. Women with childbearing potential must have a negative serum or urine pregnancy test within 7 days prior to first dose of study treatment.
- Have any prior malignancies. Patients with carcinoma in situ of any origin and patients with prior malignancies who are in remission and whose likelihood of recurrence is very low, as judged by the investigator, in consultation with the Lilly CRP, are eligible for this study. The Lilly CRP will need to approve enrollment of such patients.
- Have any condition (for example, psychological, geographical, or medical) that does not permit compliance with the study and follow-up procedures or suggest that the patient is, in the investigator's opinion, not an appropriate candidate for the study.

Alter	18 Jahre und älter
Fallzahl	15
Prüfzentren	**Krankenhaus Nordwest GmbH** (Rekrutierung beendet) Institut für klinisch-onkologische Forschung Steinbacher Hohl 2-26 60488 Frankfurt am Main Prof. Dr. med. Salah-Eddin Al-Batran Tel: 069 7601 4420 albatran@khnw.de
Sponsor	Eli Lilly and Company
Registrierung in anderen Studienregistern	ClinicalTrials.gov NCT02314117 EudraCT 2014-002240-40