# *KURZPROTOKOLL*
# *RAP*

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| **Öffentlicher Titel** | Phase II Studie zu Avelumab als Zweitlinientherapie bei gastro-ösophagealem Adenokarzinom |
| **Wissenschaftl. Titel** | Avelumab + Paclitaxel/Ramucirumab as second line treatment in gastro-esophageal adenocarcinoma: a phase II trial of the AIO |
| **Kurztitel** | RAP |
| **Studienart** | multizentrisch, prospektiv, Therapiestudie, offen/unverblindet, einarmig, Investigator Initiated Trial (IIT) |
| **Studienphase** | Phase II |
| **Erkrankung** | Verdauung: Magen-/Speiseröhrenkrebs (Magen-/Ösophaguskarzinom): Zweitlinie oder höher |
| **Einschlusskriterien** | - Signed written informed consent<br>- Male or female >= 18 years of Age<br>- Histologically proven gastric adenocarcinoma including adenocarcinoma of the esophagogastric junction<br>- Metastatic or locally advanced disease, not amenable to potentially curative resection<br>- Documented objective radiological or clinical disease progression during or within 6 months of the last dose of first-line platinum and fluoropyrimidine doublet with or without anthracycline, docetaxel or trastuzumab. Neoadjuvant/adjuvant treatment is not counted unless progression occurs <6 months after completion of the treatment. In these cases neoadjuvant/adjuvant treatment is counted as first line.<br>- Measurable or non-measurable but evaluable disease determined using guidelines RECIST 1.1<br>- Eastern Cooperative Oncology Group (ECOG) performance status 0-1<br>- Life expectancy > 12 weeks<br>- Adequate hematological, hepatic and renal functions:<br>- 1. Absolute neutrophil count (ANC) >= 1.5 x 10^9/L<br>- 2. Platelet count >= 100 x 109/L<br>- 3. Hemoglobin >= 9 g/dl (may have been transfused)<br>- 4. Total bilirubin <= 1.5 times the upper limit of normal (ULN) and AST and ALT <= 2.5 x ULN in absence of liver metastases, or <= 5 x ULN in presence of liver metastases; AP <= 5 x ULN<br>- 5. Estimated creatinine clearance >= 30 mL/min according to the Cockcroft-Gault formula (or local institutional standard method)<br>- 6. Urinary protein <= 1+ on dipstick or routine urinalysis (UA; if urinedipstick or routine analysis is >= 2+, a 24-hour urine collection for protein must demonstrate < 1000 mg of protein in 24 hours to allow participation in this protocol)<br>- 7. Adequate coagulation function as defined by International Normalized Ratio (INR) <= 1,5 ULN, and a partial thromboplastin time (PTT) <= 5 seconds above the ULN (unless receiving anticoagulation therapy). Patients receiving warfarin/phenprocoumon must be switched to low molecular weight heparin and have achieved stable coagulation profile prior to first dose of protocol therapy.<br>- Women of child-bearing potential must have a negative urine or serum pregnancy test<br>- Highly effective contraception for both male and female subjects throughout the study and for at least 30 days after last avelumab and at least 3 months after last ramucirumab treatment administration if the risk of conception exists<br>- Ability to comply with scheduled assessments and with management of toxicities. |

**Ausschlusskriterien**

- Other tumor type than adenocarcinoma (e.g. leiomyosarcoma, lymphoma) or a second cancer except in patients with squamous or basal cell carcinoma of the skin or carcinoma in situ of the cervix that has been effectively treated. Patients curatively treated for any other malignancy and disease-free for at least 5 years will be discussed with the sponsor before inclusion
- Concurrent chronic systemic immune therapy, chemotherapy, or hormone therapy not indicated in the study protocol
- Previous therapy with, paclitaxel or ramucirumab or pretreatment with a PD-1, PD-L1 Inhibitor
- Current treatment with any anti-cancer therapy <= 2 weeks prior to study treatment start unless rapidly progressing disease is measured
- Previous exposure to a VEGF (vascular endothelial growth factor) or VEGFR inhibitor or any antiangiogenic agent, or prior enrolment in this study
- Major surgical procedure, open biopsy or significant traumatic injury within 4 weeks prior to start of study treatment; anticipation of need for major surgical procedure (e.g. impending bowel obstruction) during the course of the study
- Grade 3-4 GI bleeding within 3 months prior to enrollment
- History of deep vein thrombosis (DVT), pulmonary embolism (PE), or any other significant thromboembolism (venous port or catheter thrombosis or superficial venous thrombosis are not considered "significant") during the 3 months prior to first dose of protocol therapy
- Cirrhosis at a level of Child-Pugh B (or worse) or cirrhosis (any degree) and a history of hepatic encephalopathy or clinically meaningful ascites resulting from cirrhosis. Clinically meaningful ascites is defined as ascites from cirrhosis requiring diuretics or paracentesis
- Known brain or leptomeningeal metastases
- Known prior severe hypersensitivity to investigational product or any component in its formulations, including known severe hypersensitivity reactions to monoclonal antibodies (NCI CTCAE v5.0 Grade >= 3)
- Other serious illness or medical conditions prior to study drug administration
- 1. Clinically significant (i.e., active) cardiovascular disease: cerebral vascular accident/stroke (< 6 months prior to enrollment), myocardial infarction (< 6 months prior to enrollment), unstable angina, congestive heart failure (>= New York Heart Association Classification Class II), or serious cardiac arrhythmia requiring medication
- 2. Uncontrolled or poorly controlled hypertension despite optimal medical therapy
- 3. Current history of chronic diarrhea
- 4. Active disseminated intravascular coagulation
- 5. History of gastrointestinal perforation, fistulae or any clinically relevant arterial thromboembolic event within 6 months
- 6. Active infection that, in the opinion of the investigator, may increase the risk associated with study participation, study drug administration, or would impair the ability of the subject to receive study drug
- 7. Hepatitis B virus (HBV) or hepatitis C virus (HCV) infection at screening (positive HBV surface antigen or HCV RNA if anti-HCV antibody screening test positive)
- 8. Active autoimmune disease that might deteriorate when receiving an immuno-stimulatory agent. Patients with diabetes type I, vitiligo, psoriasis, or hypo- or hyperthyroid diseases not requiring immunosuppressive treatment are eligible
- 9. Serious or non-healing wound, ulcer, or bone fracture within 28 days prior to first dose of protocol therapy

- 10. Prior organ transplantation including allogenic stem-cell transplantation
- 11. Other severe acute or chronic medical conditions including immune colitis, inflammatory bowel disease, immune pneumonitis, pulmonary fibrosis or psychiatric conditions including recent (within the past year) or active suicidal ideation or behavior; or laboratory abnormalities that may increase the risk associated with study participation or study treatment administration or may interfere with the interpretation of study results and, in the judgment of the investigator, would make the patient inappropriate for entry into this study
- Current use of immunosuppressive medication, EXCEPT for the following:
- 1. intranasal, inhaled, topical steroids, or local steroid injection (e.g., intra-articular injection);
- 2. steroids as premedication for hypersensitivity reactions (e.g., CT scan premedication)
- 3. short term steroids to prevent chemotherapy induced Nausea
- The patient is receiving chronic antiplatelet therapy, including aspirin, nonsteroidal anti-inflammatory drugs (NSAIDs, including ibuprofen, naproxen, and others), dipyridamole or clopidogrel, or similar agents. Once-daily aspirin use (maximum dose 325 mg/day) is permitted
- Vaccination within 4 weeks of the first dose of avelumab and while on trial is prohibited except for administration of inactivated vaccines
- Subjects with interstitial lung disease that is symptomatic or may interfere with the detection or management of suspected drug-related pulmonary toxicity
- Concurrent treatment with other experimental drugs or participation in another clinical trial with any investigational drug within 30 days but at least 5 half-lives of the IMP prior to treatment start
- Known drug abuse/ alcohol abuse
- Persisting toxicity related to prior therapy (NCI CTCAE v. 5.0 Grade > 1); however, alopecia, sensory neuropathy Grade <= 2, or other Grade <= 2 not constituting a safety risk based on investigator's judgment are acceptable
- Subject pregnant or breast feeding, or planning to become pregnant within 3 months after the end of Treatment
- Subject (male or female) is not willing to use highly effective methods of contraception (per institutional standard) during treatment and for 30 days (male or female) with avelumab and 3 months with ramucirumab after the end of Treatment
- Patients known to have a HER2 positive cancer who have not been treated already with a HER2 targeting Agent
- Patients with a psychiatric illness or patients imprisoned or working in the Institution of the treating physician

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| **Alter** | 18 Jahre und älter |
| **Sponsor** | Universitätsmedizin Berlin, Charite |
| **Förderer** | Merck KGaA |
| **Registrierung in anderen Studienregistern** | ClinicalTrials.gov NCT03966118 (primäres Register)<br>EudraCT 2018-002938-20 |