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| CONDITION | Pancreatic neuroendocrine tumors (pNET) |
| OBJECTIVE(S) | The aim of this study is to investigate whether ramucirumab in combination with dacarbacine has an effect on the disease-control rate at 6 months in patients with progressive pancreatic NET. |
| INTERVENTION(S) | During the study each patient with progressive PNET will receive chemotherapy with DTIC (650mg/m$^2$ d1 every 4 weeks iv) plus ramucirumab (8mg/kg d1 + d15 iv) |
| KEY EXCLUSION CRITERIA | • Pregnancy (positive urin or blood pregnancy test) or lactation.<br>• Secondary malignancy in patient's history with the exception of: disease-free period > 5 years before randomization or non-melanoma skin cancer or curatively treated cervical carcinoma in situ or other noninvasive in situ neoplasm.<br>• Allergy against dacarbazine or ramucirumab<br>• Current enrolment or participation within the last 4 weeks in a clinical drug trial<br>• Any arterial thromboembolic events, including but not limited to myocardial infarction, transient ischemic attack, cerebrovascular accident, or unstable angina, within 6 months prior to first dose of protocol therapy.<br>• Insufficient liver function: 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.<br>• Uncontrolled or poorly-controlled hypertension (>160 mmHg systolic or > 100 mmHg diastolic for >4 weeks) despite standard medical management<br>• 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<br>• Grade 3-4 GI bleeding within 3 months prior to first dose of protocol therapy.<br>• 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<br>• Uncontrolled severe physical or mental disorders such as: neurological or psychiatric disorders including seisure, advanced dementia, psychosis, active uncontrolled infections or sepsis, HIV, replicative hepatitis B or C infection<br>• History of gastrointestinal perforation/fistula (within 6 months of first dose of protocol therapy) or risk factors for perforation.<br>• Major surgery within 28 days prior to first dose of protocol therapy, or minor surgery/subcutaneous venous access device placement within 7 days prior to first dose of protocol therapy. Elective or planned major surgery to be performed during the course of the clinical trial.<br>• Serious or nonhealing wound, ulcer, or bone fracture within 28 days prior to first dose of protocol therapy. |
| KEY INCLUSION CRITERIA | • Histologically confirmed unresectable metastatic G1-G2 differentiated PNET excluding neuroendocrine carcinomas (NEC). Both non-functional and functional NET can be included.<br>• Age: 18-75 years<br>• Measurable disease (RECIST 1.1) |

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| | • Progressive disease under treatment with either non-DTIC-based chemotherapy (e.g. 5-FU/ Streptozotocin, capecitabine), SSA analogues, everolimus or sunitinib. No prior therapy with DTIC or temozolomide is allowed. Prior TACE and SIRT are allowed with a minimum of 3 months before study entry, prior PRRT is allowed with a minimum of 12 months before study entry.<br>• If the tumor biopsy is older than 6 months in progressive disease a rebiopsy is mandatory<br>• ECOG 0-1<br>• Life expectancy > 12 weeks<br>• Adequate renal function (serum creatinine ≤1.5 x ULN, or creatinine clearance (measured via 24-hour urine collection) ≥40 mL/minute (if serum creatinine is >1.5 x ULN, a 24-hour urine collection to calculate creatinine clearance must be performed). Urinary protein is ≤1+ on dipstick or routine urinalysis (UA; if urine dipstick 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>• Adequate hepatic function (total bilirubin ≤1.5 mg/dL (25.65 µmol/L), and aspartate transaminase (AST) and alanine transaminase (ALT) ≤ 3.0 x ULN; or 5.0 x ULN in the setting of liver metastases)<br>• Adequate bone marrow function (absolute neutrophil count >1,500/mm$^3$, platelets >100,000/mm$^3$, hemoglobin>9 g/dL)<br>• Adequate coagulation function (INR ≤1.5 and PTT ≤ 5 seconds above the ULN (unless receiving anticoagulation therapy). Patients receiving warfarin must be switched to low molecular weight heparin and have achieved stable coagulation profile prior to first dose of protocol therapy.<br>• Pathological condition present that carries a high risk of bleeding (for example, tumor involving major vessels or known varices)<br>• The patient, if sexually active, must be postmenopausal, surgically sterile, or using effective contraception (hormonal or barrier methods, Pearl Index <1). Female patients of childbearing potential must have a negative serum pregnancy test within 7 days prior to first dose of protocol therapy.<br>• Written informed consent |
| OUTCOME(S) | Primary endpoint<br>• Disease-control rate (DCR) at 6 months as assessed by RECIST 1.1 criteria<br>Secondary endpoints<br>• Objective tumor response (ORR)<br>• progression-free survival (PFS)<br>• overall survival (OS)<br>• toxicity<br>• biochemical response (tumor marker chromogranin A; in cases of functional NET: gastrin, insulin etc.)<br>• QoL (EORTC QLQ-C30 questionnaire)<br>• translational research for predictive biomarkers (e.g. circulating VEGF, ANGPT1/2 and IL8 levels, immunohistochemical VEGFR2 expression) |
| STUDY TYPE | Prospective single-arm multi-center phase IIa trial |
| STATISTICAL ANALYSIS | This trial is planned as a pilot study to evaluate the efficacy of combination treatment of ramucirumab and dacarbazine.<br>Primary endpoint is the disease-control rate (DCR) at 6 months as assessed by RECIST 1.1 criteria<br>The sample size calculation follows an exact binomial single-stage design (A'Hern 2001)<br>$H_0$: $p<=p_0=60\%$ versus $H_1$: $p>=p_1=80\%$, alpha=0.05, beta=0.1<br>The design requires 45 subjects recruited to decide whether the disease control rate, *p*, is less than or equal to *p0* = 60% or greater than or equal to *p1* = 80%.<br>Disease control rate (DCR) and two-sided 95% confidence intervals will be calculated (DCR = percentage of patients with CR, PR or SD and binomial proportion confidence interval). |

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| SAMPLE SIZE | To be allocated to trial: 46 |
| TRIAL DURATION | Recruitment period: 12 months<br>Treatment per patient: until disease progression or intolerable toxicity<br>Follow-up per patient: 24 months after begin of treatment.<br>First patient in to last patient out (months): 36<br>Duration of the entire trial (months): 42 months<br>Intended start date: 1st quarter 2018<br>Expected end of the study: 3rd quarter 2021 |
| PARTICIPATING CENTERS | - UK Halle<br>- UKE Hamburg<br>- Zentralklinik Bad Berka<br>- Charité<br>- UKGM Standort Marburg<br>- UK Ulm<br>- UK Göttingen |