KURZPROTOKOLL
Axitinib (AXI-IIG-02)

Öffentlicher Titel	Phase II/III Studie zu Axitinib bei fortgeschrittenen neuroendokrinen Tumoren
Wissenschaftl. Titel	Phase II/III randomized, double-blind study of Sandostatin LAR in combination with Axitinib versus Sandostatin LAR in combination with Placebo in patients with progressive advanced G1-G2 (WHO 2010) neuroendocrine tumors of non-pancreatic origin
Kurztitel	Axitinib (AXI-IIG-02)
Studienart	Therapiestudie, randomisiert, doppelblind, zweiarmig, kontrolliert, Investigator Initiated Trial (IIT)
Studienphase	Phase II/III
Erkrankung	Drüsen/Hormone/Stoffwechsel: Neuroendokrine Tumoren
Einschlusskriterien	- Histologically confirmed G1-G2 neuroendocrine tumors (per WHO 2010 classification) of non-pancreatic origin, both functioning and nonfunctioning. - Metastatic or locally advanced disease not amenable to treatment with curative intent. - Clinical or radiological progressive disease documented within 12 months prior to study entry. - Patient must have at least one measurable lesion as defined by RECIST 1.1 criteria. Patients mustn‘t have previously undergone ablative local procedures (embolization, cryoablation, radiofrequency ablation or others) within previous 6 months unless other target lesions are present or imaging progression disease is clear after those treatments (in these cases at least one month interval after local treatment is required). - Ki-67less than 20%. - Prior treatment with somatostatin analogues permitted. - Prior interferon therapy allowed. - Up to two prior lines of systemic antineoplastic medical therapy permitted other than SSA or IFN (such as chemotherapy or targeted agents excluding those targeting VEGF/VEGFR). Treatment with SSA or IFN does not count as prior lines of systemic antineoplastic therapy. - No prior VEGF- or VEGFR-targeted therapy allowed. - Adequate organ function, in terms of the values of : - 1. Absolute neutrophil count - 2. Platelet count - 3. Hemoglobin - 4. Alanine aminotransferase (ALT/SGPT) and aspartate aminotransferase (AST/SGOT) - 5. Total serum bilirubin - 6. Serum creatinine or estimated creatinine clearance - 7. Proteinuria - Male or female, age above or equal 18 years. - ECOG performance status of 0-2. - Life expectancy of above 12 weeks. - At least 4 weeks since the end of prior systemic treatment with resolution of all treatment-related toxicity to NCI CTCAE Version 4.0 grade less or equal to 1 or back to baseline except for alopecia or adequately treated hypothyroidism. - No evidence of preexisting uncontrolled hypertension as documented by 2 baseline blood pressure readings taken at least 1 hour apart. Patients whose hypertension is controlled by antihypertensive therapies are eligible.

- Women (or their partners) should be sterilized by surgical methods or be postmenopausal, or should be willing to use an effective contraceptive method while they receive the study treatment and at least for 6 month following. Women of childbearing potential must have a negative serum or urine pregnancy test within 7 days prior to treatment. Men (or their partners) should be sterilized by surgical methods or should be willing to use an effective contraceptive method while they receive the study treatment and at least for 6 month following. The definition of an effective contraceptive method should be in agreement with local regulation and based on the judgement of principal investigator or a designated associate. Lactating women will not be allowed to participate.
- Signed and dated informed consent document indicating that the patient (or legally acceptable representative) has been informed of all pertinent aspects of the trial prior to enrollment.
- Willingness and ability to comply with scheduled visits, treatment plans and study procedures (including the willingness to take axitinib or placebo according to randomization), laboratory tests and other study procedures.

Ausschlusskriterien

- The following endocrine tumor types may not be included: paraganglioma, adrenal, thyroid, parathyroid or pituitary endocrine tumors.
- Major surgery in <4 weeks or radiation therapy <2 weeks prior to starting the study treatment. Prior palliative radiotherapy to metastatic lesion(s) is permitted, provided there is at least one measurable lesion that has not been irradiated.
- Gastrointestinal abnormalities including:
- 1. inability to take oral medication;
- 2. requirement for parenteral nutrition;
- 3. prior surgical procedures affecting absorption including total gastric resection;
- 4. active peptic ulcer disease in the past 6 months;
- 5. active gastrointestinal bleeding, unrelated to cancer, as evidenced by hematemesis, hematochezia or melena in the past 3 months without evidence of resolution documented by endoscopy or colonoscopy;
- 6. malabsorption syndromes.
- Current use or anticipated need for treatment with drugs that are known potent CYP3A4 inhibitors (ie, grapefruit juice, verapamil, ketoconazole, miconazole, itraconazole, erythromycin, telithromycin, clarithromycin, indinavir, saquinavir, ritonavir, nelfinavir, lopinavir, atazanavir, amprenavir, fosamprenavir and delavirdine)unless it can be replaced by other drugs with minimal inhibition potential of CYP3A4/5. Low dose oral steroid therapy is allowed (< 5 mg/day or prednisone or equivalent). Co-administration may increase plasma concentrations of axitinib.
- Current use or anticipated need for treatment with drugs that are known CYP3A4 or CYP1A2 inducers (ie, carbamazepine, dexamethasone, felbamate, phenobarbital, phenytoin, amobarbital, nevirapine, primidone, rifabutin, rifampin, and St.John's wort), unless it can be replaced by other drugs with minimal induction potential of CYP3A4. Co-administration may decrease plasma concentrations of axitinib 6. Requirement of anticoagulant therapy with oral vitamin K antagonists. Low-dose anticoagulants for maintenance of patency of central venous access devise or prevention of deep venous thrombosis is allowed. Therapeutic use of low molecular weight heparin is allowed.
- Requirement of anticoagulant therapy with oral vitamin K antagonists. Low-dose anticoagulants for maintenance of patency of central venous access devise or prevention of deep venous thrombosis is allowed. Therapeutic use of low molecular weight heparin is allowed.
- History of relevant haemorrhage within the past 6 months, including gross hemoptysis or hematuria. Except is caused by a trated cause

	- Active seizure disorder or evidence of brain metastases, spinal cord compression, or carcinomatous meningitis. - A serious uncontrolled medical disorder or active infection that would impair their ability to receive study treatment. - Any of the following within the 12 months prior to study drug administration: myocardial infarction, uncontrolled angina, coronary/peripheral artery bypass graft, symptomatic congestive heart failure, cerebrovascular accident or transient ischemic attack and 6 months for deep vein thrombosis or pulmonary embolism. - Ongoing cardiac dysrhythmias of NCI CTCAE grade > 2, atrial fibrillation of any grade, or QTc interval >450 msec for males or >470 msec for females. - Known human immunodeficiency virus (HIV) or acquired immunodeficiency syndrome (AIDS)-related illness. - History of a malignancy (other than renal cell cancer) except those treated with curative intent for skin cancer (other than melanoma), in situ breast or in situ cervical cancer, or those treated with curative intent for any other cancer with no evidence of disease for 5 years. - Dementia or significantly altered mental status that would prohibit the understanding or rendering of informed consent and compliance with the requirements of this protocol. - Other severe acute or chronic medical or psychiatric condition, or laboratory abnormality that may increase the risk associated with study participation or study drug 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, recent (within 4 weeks of the study treatment administration), or planned participation in an experimental therapeutic drug study other than this protocol.
Alter	18 Jahre und älter
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Sponsor	Grupo Español de Tumores Neuroendocrinos
Förderer	Pfizer
Registrierung in anderen Studienregistern	ClinicalTrials.gov NCT01744249 (primäres Register) EudraCT 2011-001550-29