Unresectable Adrenocortical Carcinoma

AIO-ENC-0118/ass - A Single center, Open-label, Phase II Study to Evaluate the Efficacy and Safety of Cabozantinib in Advanced (Unresectable or Metastatic) Adrenocortical Carcinoma (CaboACC)

AIO-assoziierte Studie	
Studiennummer/-Code:	AIO-ENC-0118/ass - CaboACC
Status:	Rekrutierend
Rekrutierungszeitraum:	2019 – 2024
Patienten:	geplant: 37 (min. 29) aktuell eingeschlossen: 29
Weitere Zentren:	Nicht geplant (2 Zentren)
Letzte Aktualisierung	10/2023

Art der Studie Study Type	Prospective multicenter open label phase-II	
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Studienziele/ Objectives	To determine the efficacy and safety of cabozantinib as a treatment for unresectable/advanced adrenocortical carcinoma. To explore the relationship between cabozantinib pharmacokinetics and treatment response and tolerability To study steroid hormone biomarkers and targeted metabolomics as markers of disease response. To study the effect of cabozantinib on immune markers by obtaining blood samples collection at baseline, during therapy and at time of progression. To explore the relation between pharmacogenetic variants and cabozantinib pharmacokinetics.	

	To explore the relation of c-MET copy number (FISH), mutations (incl. ΔExon14), c-MET mRNA expression (RNAscope) and VEGFR2 expression (IHC) and response in archival formalin-fixed paraffin-embedded tissue specimens To characterise pre-defined populations of immune cells, immune cell differentiation status and functionality in available fresh/fresh frozen tumor specimens
Zielparameter/ Objectives	Primary end point: - progression free survival at 4 months Secondary end points: - overall survival - Best Objective Response Rate (ORR) - duration of response (DR) - progression-free survival - best percentage change in size of target lesions - incidence and severity of adverse events possibly related to cabozantinib graded according to CTC-AE 4.03 - quality of life by EORTC QLQ-C30 Exploratory - steady-state trough plasma concentration of cabozantinib by quantile - biochemical response: defined as reduction of one or more marker steroids in urine or plasma by >50% at any time (excluding patients treated with inhibitors of steroidogenesis concomitantly). - control of cortisol excess: defined as normalization of elevated urinary free cortisol at baseline at any time (excluding patients treated with inhibitors of steroidogenesis concomitantly) - change from baseline of pre-specified immune cell markers at during treatment - correlation of steady state trough cabozantinib plasma concentration with pre-specified variants of enzymes of drug metabolism and disposition - descriptive analysis of expression of tissue markers and response
Patientenzahl Number of patients	Planned: 37 Already included: 29 (37 screened)
period of trial	2019 – 2024
More centres?	multi-center trial
Haupt-Einschlusskriterien / Key inclusion criteria	1. ≥ 18 years old on the day of consent 2. histological confirmation of ACC 3. Locally advanced or metastatic disease not amenable to surgery with curative intent with measurable disease per RECIST 1.1 within 28 days before the first dose of cabozantinib 4. Eastern Cooperative Oncology Group (ECOG) performance status of 0-2 5. Recovery to baseline or ≤ Grade 1 CTCAE v.4.0 from toxicities related to any prior treatments, unless AE(s) are clinically non-significant and/or stable on supportive therapy 6. Life expectancy of at least 3 months 7. Organ and bone marrow function and laboratory values within pre- 8. Capable of understanding and complying with the protocol requirements. 9. Sexually active patients of reproductive potential (men and women) must agree to use medically accepted barrier methods of contraception (e.g. male or

	female condom) during the course of the study and for 4 months after the last dose of study drug(s), even if oral contraceptives are also used. 10. Able to give written informed consent
Haupt-Ausschlusskriterien Key exlusion criteria	1. cytotoxic chemotherapy, radiation therapy, or targeted therapy (including investigational cytotoxic chemotherapy) or biologic agents (e.g., cytokines or antibodies), or other investigational agent within 28 days of study enrollment. 2. Treatment with mitotane <28 days prior study inclusion OR mitotane serum/plasma con-centration documented of ≥2 mg/L. 3. Prior treatment with cabozantinib or other cMET inhibitors 4. Known brain metastases or cranial epidural disease unless adequately treated with radio-therapy and/or surgery (including radiosurgery) and stable for at least 4 weeks before the first dose of study treatment. Eligible subjects must be neurologically asymptomatic and without corticosteroid treatment at the time of the start of study treatment. 5. Prothrombin time (PT)/ International Normalized Ratio (INR) or partial thromboplastin time (PTT) test ≥1.3 × the laboratory ULN within 28 days before the first dose of study treat-ment. 6. Concomitant anticoagulation with oral anticoagulants (e.g., warfarin, direct throm-bin and Factor Xa inhibitors), platelet inhibitors (e.g., clopidogrel) or therapeutic doses of low molecular weight heparins (LMWH). Low dose aspirin for cardioprotection (per local applicable guidelines) and low dose LMWH are permitted. Anticoagulation with therapeutic doses of LMWH is allowed in subjects who are on a stable dose of LMWH for at least 6 weeks before the first dose of study treatment, and who have had no clinically significant hemorrhagic complications from the anticoagulation regimen or the tumor. 7. The use of strong CYP3A4 inhibitors (with the exception of ketoconazole). 8. The subject has experienced any of the clinical conditions defined in the full protocol 9. evidence of tumor invading the GI tract (esophagus, stomach, small or large bowel, rec-tum or anus), or any evidence of endotracheal or endobronchial tumor within 28 days before the first dose of cabozantinib, or the subject with radiographic evidence of cavitating pulmonary lesion(s); or subjects with tumor invading or encasing any major blood vessels. 10. Uncontrolled, significant concurrent or recent illness or disorders as specified in the protocol. 11. Any of the following within 6 months before the first dose of study treatment: • abdominal fistula • gastrointestinal perforation • bowel obstruction or gastric outlet obstruction • intra-abdominal abscess 12. Unable to swallow tablets 13. QTcF>500 milliseconds within 28 days before first dose of study 17. Pregnancy or breastfeeding. 18. A previously identified allergy or hypersensitivity to components of the study treatment formulation. 19. Unable or unwilling to abide by the study protocol or cooperate fully with the investigator or designee. 20. Evidence within 2 years of the start of study treatment of another malignancy which re-quired systemic treatment except for breast ductal carcinoma-in situ, cured non-melanoma skin cancer, or cured in situ cervical carcinoma 21. Any other severe acute or chronic medical or psychiatric condition or laboratory abnormality which, in the judgment of the investigator, would have made the patient inappropriate for entry into this study.
Therapieschema Scheme of therapy	Cabozantinib tablets 60 mg qd.

Tumorevaluierung Criteria for evaluation	RECIST1.1
Rationale	Adrenocortical carcinoma (ACC) is a rare endocrine malignancy with poor prognosis and limited response to therapy. Recurrence after surgical resection is very common in patients presenting with localized disease and systemic therapy is the primary treatment for patients with recurrent or advanced disease. The combination of cisplatin/etoposide/doxorubicin/mitotane is the current standard of care for metastatic ACC (Fassnacht et al., NEJM 2012). This combination has a suboptimal response rate of 23% with median time to progression of about 5 months while second line therapy (streptozocin with mitotane) has response rate of 9% with median time to progression of about 2 months. In vitro evidence demonstrated increased HGF/cMET expression in human ACC samples (Phan et al, Cancer Res 2015) and in vitro data point to cMET up-regulation as a mechanism of drug resistance. A case series of seven ACC patients refractory to standard treatment with cabozantinib showed partial remission in two, SD in two and progressive disease in two patients. The median progression-free survival was 20 weeks and overall survival 58 weeks. Treatment was overall well tolerated with no treatment emergent serious adverse events. The results of this retrospective study are remarkable in that all patients had progressed to prior mitotane and 1-8 additional systemic therapies and compares favorably with the poor prognosis of most patients with advanced ACC.
Statistik (optional)	The primary analysis is the analysis of the binary primary endpoint progression-free survival at 4 months (PFS4) in the two-stage Simon design. Point estimation for the underlying rate of PFS4 by the uniformly minimum variance unbiased estimator (UMVUE), p-value for testing in Simon's two-stage design and two-sided 90% confidence interval according to Koyama & Chen (2008). Sample size calculation according to the algorithm of Simon for two-stage phase II trials: Based on these results of Kroiss et al. (2012) and Fassnacht et al. (2015) and on clinical experience we consider p0 = 0.05 (5%) as the largest proportion for PFS at 4 months which, if true, implies that Cabozantinib is not warrant further investigation. Furthermore we consider p1 = 0.20 (20%) as the smallest proportion which, if true, implies that Cabozantinib is promising and warrants further investigation. Requirements for testing the null hypothesis H0 that the underlying proportion of patients with PFS at 4 months is ≤ p0 = 0.05: The sample size has to be sufficiently large to ensure that the probability for rejecting H0 if in fact H0 is true (that means p ≤ 0.05) is 0.05 as well as the probability for rejecting H0 if in fact p ≥ p1 = 0.20 holds, is 0.80. Then the optimal Simon two-stage design requires a maximum of 29 ACC patients with progressing disease after standard therapy. After evaluation of the primary endpoint for 10 patients in the first stage the trial will be terminated because of futility (insufficient efficacy) if none patient has survived progression-free at 4 months. Otherwise the trial goes on the second stage and a total of 29 patients will be studied. If the total number of patients with PFS at 4 months is less than or equal to 3 the null hypothesis of insufficient efficacy (that means ≤ p0 = 0.05), is not rejected. Assuming a drop-out rate of 20% within 4 months 37 patients have to be included in the study. Sample size calculation was done with the software PASS14 (NCSS). For the time-to-event endpoints progression-free survival (PFS), overall survival (OS) as well as duration of complete response (CR) and partial response (PR) the 'survival' functions will be estimated by the Kaplan-Meier product-limit estimator. From this unbiased descriptive statistics, e.g. median 'survival' time, will be estimated.