AIO-HEP-0320/ass: A phase II study evaluating reduced starting dose and dose escalation of Cabozantinib as second-line therapy for advanced HCC in patients with preserved liver function (CaboRISE)

AIO-assoziierte Studie

Studiennummer/-Code:	**AIO-HEP-0320/ass_CaboRISE**
Status:	aktiv
Rekrutierungszeit:	Studienstart Q4 2020, Rekrutierungszeit 36 Monate
Anzahl Zentren:	geplant: 10 aktuell initiiert: 11 aktiv rekrutierend: 8
Weitere Zentren:	Nicht geplant
Anzahl Patienten:	geplant: 40 aktuell eingeschlossen: 31 (FPI 12.10.2020)
Letzte Aktualisierung	07/2023

APPLICANT/ COORDINATING INVESTIGATO	Prof. Dr. med. Jörg Trojan Universitätsklinikum Frankfurt Goethe-Universität Medizinische Klinik 1 Theodor-Stern-Kai 7 60590 Frankfurt/Main
CONDITION	Advanced stage hepatocellular carcinoma (HCC) patients with preserved liver function in second line therapy
OBJECTIVE(S)	The primary objective is to assess the tolerability of a reduced starting dose of 40 mg cabozantinib once-daily for 4 weeks and subsequent dose escalation to 60 mg cabozantinib once-daily to be maintained until disease progression or intolerable toxicities in patients with advanced stage hepatocellular carcinoma (HCC) with preserved liver function in second line therapy.
INTERVENTION(S)	Cabozantinib 20 mg/day // Cabozantinib 40 mg/day // Cabozantinib 60 mg/day
KEY EXCLUSION CRITERIA	1. Pregnancy or breastfeeding, or intention of becoming pregnant during study treatment or within at least 4 months. 2. Significant portal hypertension (moderate or severe ascites). Significant hypertension, defined as blood pressure ≥ 140 mmHg (systolic) or ≥ 90 mmHg (diastolic) in repeated measurements. 3. Known fibrolamellar HCC, sarcomatoid HCC, or mixed cholangiocarcinoma and HCC. 4. Patients with impaired liver function defined as Child-Pugh B or C, if liver cirrhosis is present. 5. Severely impaired kidney function (defined as creatinine > 2 mg/dl and/or creatinine clearance < 45 mL/min). 6. Elevations of AST/ALT > 5 x ULN at baseline. 7. Presence of encephalopathy in past 12 months. 8. Significant cardiovascular disease (such as NYHA Class II or greater cardiac disease, myocardial infarction, or cerebrovascular accident) within 3 months prior to initiation of study treatment, unstable arrhythmia, or unstable angina. 9. Baseline QTcF > 500 ms. 10. Major surgical procedure, other than for diagnosis, within 4 weeks prior to initiation of study treatment, or anticipation of need for a major surgical procedure during the study.

	11. Severe infection within 4 weeks prior to initiation of study treatment, including, but not limited to, hospitalization for complications of infection, bacteremia, or severe pneumonia. 12. Any other disease, metabolic dysfunction, physical examination finding, or clinical laboratory finding that contraindicates the use of an investigational drug, may affect the interpretation of the results, or may render the patient at high risk from treatment complications. 13. Treatment with investigational systemic therapy within 28 days or five times the elimination half-life of the investigational product, whichever is longer, prior to initiation of study treatment. 14. Prior cabozantinib use. 15. Known or suspected hypersensitivity to cabozantinib or any other excipients of the IMP. 16. Rare hereditary galactose intolerance, total lactase deficiency or glucose-galactose malabsorption. 17. Is currently participating in or has participated in a study of an investigational agent or has used an investigational device within 4 weeks prior to the first dose of study treatment. 18. Patient who has been incarcerated or involuntarily institutionalized by court order or by the authorities § 40 Abs. 1 S. 3 Nr. 4 AMG. 19. Patients who are unable to consent because they do not understand the nature, significance and implications of the clinical trial and therefore cannot form a rational intention in the light of the facts [§ 40 Abs. 1 S. 3 Nr. 3a AMG].
KEY INCLUSION CRITERIA	1. Fully informed written consent. 2. Males and females ≥ 18 years of age. *There are no data that indicate special gender distribution. Therefore, patients will be enrolled in the study gender-independently. 3. Patients with HCC who have been previously treated with any first line therapy. 4. Locally advanced or metastatic and/or unresectable HCC with diagnosis confirmed by histology/ cytology or clinically by guideline criteria in cirrhotic patients. 5. Disease that is not amenable to curative surgical and/or locoregional therapies, or progressive disease after surgical and /or locoregional therapies. 6. Resolution of any acute, clinically significant treatment-related toxicity from prior therapy to Grade 1 prior to study entry, with the exception of alopecia. 7. ECOG performance status ≤ 2. 8. Women of childbearing potential must have a negative serum pregnancy test result within 14 days prior to initiation of study treatment. 9. For women of childbearing potential: agreement to remain abstinent (refrain from heterosexual intercourse) or use highly effective contraceptive methods from the time of signing the informed consent through at least 4 months after the last dose of study drug or agree to completely abstain from heterosexual intercourse. Male patients, even if surgically sterilized (i.e. status post-vasectomy) must agree to practice effective barrier contraception (e.g. condom) and to refrain from sperm donation during the entire study treatment period and through at least 4 months after the last dose of study drug or agree to completely abstain from heterosexual intercourse.
OUTCOME(S)	<u>Primary endpoint</u>: Treatment discontinuation rate due to treatment-related adverse events. <u>Secondary endpoints:</u> • Overall survival (OS)

	• Progression free survival (PFS) at 10 weeks • Objective response rate (ORR) • Time on treatment • Treatment exposure (dose intensity/dose reductions) • Toxicity • QoL (QLQ-C30) • Correlation of biomarkers potentially associated with clinical efficacy (OS, PFS and ORR) <u>Translational Research:</u> FFPE tissue for future translational research projects are being collected upon the patient's consent only. Translational research projects are not per-determined by this protocol and will be defined taking latest research data into account. The TR might include the assessment of the following: • FFPE tissue for IHC staining; • FFPE tissue for nucleic isolation to assess the expression of biomarkers, determination of genetic alterations in HCC (panel sequencing) or to determine the mutational load.
STUDY TYPE	Open-label, single-arm, multicenter phase II trial
STATISTICAL ANALYSIS	Based on the study by Abou-Alfa [Abou-Alfa et al., 2018], the rate of Cabozantinib treatment discontinuation for toxicity is 16%. Our hypothesis is that therapy optimization using a lower starting dose would reduce the rate of treatment discontinuation or toxicity to 10% or lower, which is a reasonable aim, and is considered to be a clinically relevant advantage. On the other hand, efficacy will not be impaired as more patients will be able to maintain the planed doses. The study is exploratory and has no formal, power-based sample size calculation. The primary endpoint is the rate of treatment discontinuation for toxicity. Because only the highest rate of discontinuation for toxicity is of interest, the tests are one-sided. Enrolling 40 patients would result in an upper 90% confidence interval (CI) limit of 16.3% for the expected discontinuation rate, which is similar to mean rate seen with the standard dose regimen and is considered acceptable for an exploratory trial. Secondary endpoints are overall survival, progression-free survival, and dose reductions. The primary population for the analyses consists of all registered patients (intention-to-treat). A per-protocol population will be prospectively defined for sensitivity analyses, based on the amount of treatment actually received according to protocol. The primary endpoint is defined as the number of patients with treatment discontinuation for toxicity divided by the number of all patients enrolled. The secondary endpoints PFS and OS will be analyzed using the Kaplan-Meier method.
SAMPLE SIZE	40 patients
TRIAL DURATION	Overall study duration: 50 months
PARTICIPATING CENTERS	11 centers