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SPONSOR	Universitätsmedizin Mainz
CONDITION	Advanced Hepatocellular Carcinoma (HCC)
DESIGN	Phase I/II multicenter, open-label, single arm Study
INDICATION	HCC with WNT signalling alterations
OBJECTIVE(S)	Safety and efficacy of DKN01
INTERVENTION(S)	DKN01 in combination with sorafenib
OBJECTIVES of OPTIONAL TRANSLATIONAL RESEARCH	Mechanisms of DKN01 response
BACKROUND/RATIONALE	Alterations in the WNT/β-catenin signaling pathway are among the most common changes observed in liver cancer and can be considered true drivers of disease initiation and progression. Furthermore, activation of the pathway is associated with adverse clinical features (Monga, 2015). Therefore, treatment strategies targeting activity of the pathway or selected members are highly desirable. In this context, elevated expression of DKK1, a prominent member of the pathway, are observed in up to 70% of patients with HCC and associated with WNT activation and a poor clinical outcome (Andersen et al., 2010; Shen et al., 2012; Yu et al., 2009). For these reasons, the here proposed DKK1 inhibition with DKN-01 harbors great potential to improve the limited outcome of affected HCC patients with activation of the pathway. Furthermore, several lines of evidence indicate that inhibition of WNT might synergistically modulate the therapeutic potential of sorafenib in HCC. To explore the therapeutic effects of DKN-01 with and without the combination with sorafenib, therefore, seems highly promising to improve the outcome of patients with HCC.
KEY EXCLUSION CRITERIA	- Patients with the following histology of hepatocellular cancer are not eligible for enrollment: fibrolamellar carcinoma or mixed hepatocellular cholangiocarcinoma. - New York Heart Association Class III or IV cardiac disease, myocardial infarction within the past 6 months, or unstable arrhythmia. - Specific cardiac preconditions : Fridericia-corrected QT interval (QTcF) >470 msec (female) or >450 msec (male), or history of congenital long QT syndrome. Any ECG abnormality that in the opinion of the Investigator would preclude safe participation in the study; patients with pacemakers where QTc is not a reliable measure will require an evaluation by a cardiologist to exclude co-existing cardiac conditions which would prohibit safe participation in the study. - Active, uncontrolled bacterial, viral, or fungal infections, within 7 days of study entry requiring systemic therapy. - human immunodeficiency virus (HIV) positive, - History of major organ transplant (i.e., heart, lungs, liver, or kidney). - History of autologous/allogenic bone marrow transplant. - Serious non-malignant disease that could compromise protocol objectives in the opinion of the Investigator and/or Sponsor. - Pregnancy or nursing. - Major surgical procedures, open biopsy or significant traumatic injury within 4 weeks prior to treatment start (minor procedures within 1 week)

	- History of osteonecrosis of the hip or evidence of structural bone abnormalities in the proximal femur on magnetic resonance imaging (MRI) scan that are symptomatic and clinically significant. Degenerative changes of the hip joint are not exclusionary. Screening of asymptomatic patients is not required. - Symptomatic central nervous system (CNS) malignancy or metastasis. Patients with treated CNS metastases are eligible provided their disease is radiographically stable, asymptomatic, and they are not currently receiving corticosteroids and/or anticonvulsants. Screening of asymptomatic patients without a history of CNS metastases is not required. - Known osteoblastic bone metastasis. Screening of asymptomatic patients without a history of metastatic bone lesions is not required. - Medical or psychological conditions that would jeopardise an adequate and orderly completion of the trial. - Thrombotic or embolic events (except HCC tumor thrombus <pVT4) within the past 6 months (including cerebrovascular accidents) - Evidence of portal hypertension with bleeding esophageal or gastric varices within the past 6 months - Patients with portal thrombosis = pVT4 Medication Related - Prior locoregional therapy or radiation therapy within 28 days prior to first dose. - prior systemic therapy for HCC - Currently receiving any other investigational agent or received an investigational agent within last 30 days prior to first dose or within 5 times the half-life of this agent before the first dose of study treatment. - Previously treated with an anti-DKK1 therapy. - Treatment with strong inducers of CYP3A4 within 7 days prior to first dose (including Cyclosporin, Erythromycin, Ketoconazole, Itraconazole, Quinidine, Phenobarbital salt with Quinidine, Ritonavir, Valspodar, Verapamil, St John's wort, rifampicin). - Significant allergy to a pharmaceutical therapy that, in the opinion of the Investigator, poses an increased risk to the patient. - History of hypersensitivity to the investigational medicinal product or to any drug with similar chemical structure or to any excipient present in the pharmaceutical form of the investigational medicinal product. Lifestyle-Related - Active substance abuse (including active alcohol abuse). - Involuntary incarcerated patients
KEY INCLUSION CRITERIA	- Ambulatory male or female patients ≥ 18 years - Patients must have histologically confirmed diagnosis (by either primary surgical specimen or biopsy for recurrence) of advanced stage or recurrent diagnosis of HCC based on histopathologic findings. - Tumor tissue is **mandatory** for pre-treatment evaluation (baseline) (fresh biopsy during 4-weeks screening time preferred. Archived specimen is only acceptable, if ≤ 6 months old. Baseline tumor biopsy samples must be available prior to the first dose of DKN-01. - Tumor tissue (FFPE) must be received by central histopathology laboratory for correlative studies (fine needle aspiration and bone metastasis samples are not acceptable). - Patients with activated WNT/β-catenin signaling identified by glutamine synthetase staining (high positive staining in tumor tissue) by an approved lab. Positive staining must be confirmed prior to first dose of DKN-01. - Child-Pugh score <7 (Child-Pugh Class A). - Barcelona Clinic Liver Cancer (BCLC) Stage C disease or BCLC Stage B disease not amenable to resection, locoregional therapy or refractory to locoregional therapy. - At least one tumor lesion measurable on radiographic imaging as defined by mRECIST for HCC **that has not been previously** treated by locoregional therapies. - Locoregional therapies or radiation therapy must be completed at least 4 weeks prior to baseline scan. All toxic effects > grade 1 (NCI CTCAE v5.0) related to any prior HCC treatment must be resolved. Palliative radiotherapy for symptomic control is acceptable and no additional radiotherapy for the

	same lesion is planned. (like bone metastases should not be targets for RECIST). - ECOG performance status (PS) of 0 or 1. - Estimated life expectancy of at least 3 months, in the judgment of the Investigator. - Disease-free of active second/secondary or prior malignancies for ≥2 years with the exception of currently treated basal cell, squamous cell carcinoma of the skin, or carcinoma in-situ of the cervix or breast. - Patients are eligible to enroll if they have non-viral-HCC, or if they have HBV-HCC, or HCV-HCC defined as follows: o HBV-HCC: Resolved HBV infection (as evidenced by detectable HBV surface antibody, detectable HBV core antibody, undetectable HBV DNA, and undetectable HBV surface antigen) or chronic HBV infection (as evidenced by detectable HBV surface antigen or HBV DNA). Patients with chronic HBV infection must have HBV DNA < 2000 IU/mL and must be on antiviral therapy. o HCV-HCC: Active or resolved HCV infection as evidenced by detectable HCV RNA or antibody - Acceptable liver function: o Total bilirubin ≤2.0 × upper limit of normal (ULN). o Aspartate aminotransferase (AST) and alanine aminotransferase (ALT) ≤5 × ULN. - Acceptable renal function: o Calculated creatinine clearance ≥50 mL/min using the Cockcroft and Gault Method (Cockcroft and Gault 1976). - Acceptable hematologic status: o Neutrophil Granulocyte ≥1500 cells/µl. o Hemoglobin ≥ 8,5 g/dL (= 5,28 mmol/l) (transfusion permitted within 30 days of study entry). o Platelet count ≥75,000 cells/µl. - Acceptable coagulation status: o INR ≤ 1.7 and no active bleeding, (i.e., no clinically significant bleeding within 14 days prior to first dose of study therapy) - Female subjects who are post-menopausal (defined as spontaneous amenorrhea for at least a year) or permanently sterilized (e.g. bilateral oophorectomy, hysterectomy, bilateral salpingectomy) can participate in the trial and are not required to use any contraception. - Women of child bearing potential (WOCBP, a woman is considered of childbearing potential i.e. fertile, following menarche and until becoming post-menopausal) must have a negative serum or urine pregnancy test within 7 days prior to first dose of DKN-01. The minimum sensitivity of the pregnancy test must be 25 IU/L or equivalent units of HCG. - Women of childbearing potential must be willing to practice a highly effective and medically accepted contraception method during trial and for 18 months after last dose of study drug. A highly effective method of birth control is defined as one which results in a low failure rate (i.e. less than 1% per year) when used consistently and correctly such as: o combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation: ▪ oral ▪ intravaginal ▪ transdermal o progestogen-only hormonal contraception associated with inhibition of ovulation: ▪ oral ▪ injectable ▪ implantable o intrauterine device (IUD) o intrauterine hormone-releasing system (IUS) o bilateral tubal occlusion o vasectomised partner (medical assessment must be present and done) o sexual abstinence when this is in line with the preferred and usual lifestyle of the subject - Periodic abstinence (calendar, symptothermal, post-ovulation methods), withdrawal (coitus interruptus), spermicides only, and lactational

	amenorrhoea method (LAM) are not acceptable methods of contraception. Female condom and male condom should not be used together. Sexually-active male subjects must be willing to use contraception (condom, contraception for non-pregnant WOCBP partner) with their partners throughout the study and for 18 months after last dose of study drug and agree to inform the
OUTCOME(S)	Part A: Evaluation of safety and tolerability using frequency and severity of adverse events to establish the recommended phase II dose (RP2D) of DKN-01 when administered as monotherapy for 8 weeks and in combination with sorafenib for 4 weeks in adult patients with HCC. Part B: To assess the time to progression (TTP1, TTP2) in treatment naïve patients with advanced HCC after treatment with DKN-01 monotherapy until PD1 and in combination with sorafenib until PD2. TTP1 and TTP2 will be determined according to mRECIST.
STATISTICAL ANALYSIS	Definition: PD1: Progressive Disease according to mRECIST with DKN-01 monotherapy. PD2: Progressive Disease according to mRECIST with combination therapy of DKN-01 and sorafenib. Disease progression will be judged versus the status before start of sorafenib therapy. Primary analysis variable: TTP2 is defined as the time from first DKN-01 intake until PD2. Patients will be censored at study end or discontinuation of the study. The TTP2 will be analyzed by a one-sided logrank test. For the primary analysis no covariates will be considered. Moreover, TTP2 will be displayed by the median survival time and the corresponding 95% confidence interval. Kaplan Meier plots will be presented. A similar analysis for the TTP1 (time from first DKN-01 intake until PD1) will also be performed. Secondary analysis variables: - Overall survival is defined as the time from first DKN-01 intake until death from any cause. Progression free survival (PFS1, PFS2) is defined as the time from first DKN-01 intake until death or PD1 or PD2 respectively whichever comes first. Survival parameters (OS, PFS1, PFS2) will be analyzed by survival analysis methods i.e. Kaplan-Meier plots and median event time including the corresponding 95% confidence interval. ORR (CR or PR) and DCR (CR, PR or SD) after 2, 4 and 6 months will be analyzed by absolute and relative frequencies. - For duration of response (time from first to the last disease control (CR, PR, or SD)) will be displayed by descriptive statistics. - Adverse events will be coded by MedDRA terminology and analyzed by absolute and relative frequencies, DLTs will be graded according to the NCI CTCAE v4.03 Interim analysis: There will be no formal interim analysis. After each cohort (10 patients each) in Part A a safety assessment will be performed and the next dose strength will be determined. After Part A (20 patients) the safety profile will be assessed. This is an exploratory study, therefore type 1 error inflation and statistical power will not be considered after Part A.
SAMPLE SIZE	Part A 20 patients; Part B 50 patients
TRIAL DURATION	3 years
PARTICIPATING CENTERS	Mainz, Hannover, Hamburg, Frankfurt, Cologne, Mannheim, Lübeck