Report Synopsis of Study Dial-1

EudraCT-Nr.: 2017-002468-41

Vorlage-Nr.: 3287

1) **Name of Sponsor/Company:** University Medical Center of the Johannes Gutenberg-University Mainz represented by the scientific member of the executive board Univ.-Prof. Dr. U. Förstermann	4) **Individual Study Table Referring to Part of the Dossier:** na[1] Volume: na Page: na	*(For National Authority Use only)*
2) **Name of Finished Product:** *n.a*		
3) **Name of Active Substance:** *DKN-01*		

5) **Title of Study[2]:**

A phase I/II multicenter, open-label Study of DKN-01 to investigate the anti-tumor activity and safety of DKN-01 in Patients with Hepatocellular Carcinoma and WNT signaling Alterations

Eine offene, multizentrische Phase I/II-Studie zur Untersuchung der Wirksamkeit und Sicherheit von DKN-01 bei Patienten mit fortgeschrittenem Leberzellkarzinom und Veränderungen im WNT-Signaltransduktionsweg

The initial study protocol (version 1.2 dated 16-May-2018) was approved on 22-June-2018. Due to formal changes requested by PEI Protocol V1.3 dated 25-June-2018 was submitted to the ECs and approved on 23-July-2018.

Protocol V 1.4 dated 22.05.2019 and approved on 1-July-2019:

Due to new side effects reported with sorafenib: (Blood creatine phosphokinase increased, which may indicate muscle injury; Urinary retention; Vaginal haemorraghe) listed in the IB V5.0 and the addition of special warnings and precautions for use in the SMPC Nexavar June 2018 (Hypoglycemia -Reductions in blood sugar have been reported during treatment with sorafenib, which in some cases were clinically symptomatic and required hospitalization due to loss of consciousness) changes were necessary. New side effects and special warnings and precautions were listed in the protocol and Blood Creatine Phosphokinase Assessment was included due to safety assessment.

Protocol V1.5 dated 03.December-2019 approved by EC on 03- January 2020 and noted by PEI on17-January 2020:

Due to change of location of the LKP formal changes were required.

6) **Principal Investigator(s):** Prof. Dr. med. Jens Marquardt, Prof. Dr. med. Markus Möhler, PD Dr. med. Arndt Weinmann, Dr. Kornelius Schulze

7) **Study centre(s):** Only study centers that have enrolled patients are listed.

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[1] This information is only required in connection with filing of a dossier for marketing authorization.

[2] The latest protocol version must be clearly stated, this means including all amendments – the amendments are to be declared and identified.

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Universitätsklinikum Schleswig Holstein Campus Lübeck

Ratzeburger Allee 160

23538 Lübeck

8) **Publication (reference):** n.a.

9) **Studied period (years)[3]:**	10) **Phase of development:** I/II
Date of first enrolment: 10-October 2018 *Date of last completed: The clinical trial was terminated prematurely on 08-December-2021 due to slow recruitment and change in the landscape of first line standard of care therapy for HCC.*	

11) **Objectives:**

Primary Objective

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 8 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.

Secondary Objectives

Part A:

- To assess safety of the doses of 300 mg and 600 mg DKN-01 given as mono- and as combination therapy

- To characterize the pharmacokinetics of DKN-01 when administered at the dose of 300 mg and 600 mg as monotherapy and in combination with sorafenib

Part B:

- To assess tumor response with DKN-01 monotherapy and in combination with sorafenib

- To assess the clinical safety of DKN-01 monotherapy and in combination with sorafenib at the dose used for part B

- Scientific objectives: Assays to identify biomarkers of benefit from DKN-01 therapy, as well as biomarkers of DKN-01 resistance

12) **Methodology:** Prospective multicenter, open label phase I/II

13) **Number of patients (planned and analyzed):**

Planned

Part A: A maximum of 20 patients with advanced HCC with activated WNT/β-catenin signaling.

Part B: 50 patients with advanced HCC with activated WNT/β-catenin signaling

Analyzed

Part A. 8 patients were included in cohort 1 of Part A. No patients were included in Part A cohort 2 or Part B of the study.

14) **Diagnosis and main criteria for inclusion:**

Patients meeting all of the following criteria were enrolled to the trial:

[3] Here also study suspensions and premature terminations of a trial/premature conclusion of a trial should be listed, including the reasons for that.

- 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 Investigator if the respective partner becomes pregnant during this time.

- Provided written informed consent prior to any study-specific procedures.

- Ability of patient to understand nature, importance and individual consequences of this clinical trial.

15) **Test product, dose and mode of administration, batch number:**
Treatments includes both Investigational Medicinal Products (IMP) and Non-investigational Medicinal Products (Non-IMP) as listed:

Drugs for Dial-1 study		
Medication	**Potency**	**IMP/Non-IMP**
DKN-01 solution for IV	20 mg per vial	IMP
sorafenib tablets	200 mg per tablet	Non-IMP (standard of care)

Doses and mode of administration

DKN-01 was administered intravenous (IV) over a minimum of 30 minutes and up to a maximum of 2 hours given on days 1 and 15 of each 28 day cycle.

Part A (phase I):

Study treatment was started as monotherapy with DKN-01 for up to 8 weeks or until unacceptable toxicity occurs. After 8 weeks monotherapy with DKN-01, the study was continued as combination therapy of DKN-01 and sorafenib until objective disease progression (PD) or unacceptable toxicity occurs. After objective PD with combination therapy, study treatment has to be stopped. The dose of DKN-01 for cohort 1 will be 300 mg and cohort 2 will be 600 mg or 150 mg, depending on the results of the safety assessment of cohort 1. All patient that are included int hestudy were dosed at 300 mg.

Part B (phase II):

The dose of DKN-01 will be the recommended phase II dose (RP2D) determined from Part A. Study treatment will be started as monotherapy with DKN-01 until objective disease progression (PD1) or unacceptable toxicity occurs. After PD1, study treatment will be continued as combination therapy of DKN-01 and sorafenib until disease progression (PD2) or unacceptable toxicity occurs. After PD2, study treatment has been stopped.

For combination with DKN-01, sorafenib was administrated according to standard clinical practice.

***DKN-01 Drug Product Lot Number*:** *C160158*

16) **Duration of treatment:** Treatment was continued as combination therapy of DKN-01 and sorafenib until objective disease progression (PD) or unacceptable toxicity occurs.

17) **Reference therapy, dose and mode of administration, batch number:** n.a.

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18) **Criteria for evaluation[4]:**

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 was judged versus the status before start of sorafenib therapy.

Efficacy:

Part A: none

Part B: Time to progression (TTP2). The TTP2 defined as the time from the first dosing until PD2. Tumor progression was assessed by mRECIST criteria (modified Response Evaluation Criteria in Solid Tumors).

Part B: To assess

– Overall survival (OS), progression free survival (PFS1, PFS2), the objective response rate (ORR), and the disease control rate (DCR) with DKN-01 as a monotherapy and in combination with sorafenib at end of study

– Duration of disease control with DKN-01

Safety:

Part A: Absolute and relative frequencies of adverse events, Serum DKN-01 levels

Part B: Safety and tolerability of DKN-01 mono- and combination therapy with sorafenib: analysis of adverse events as assessed by NCI CTCAE v5.0 and laboratory data

19) **Statistical methods:**

Part A: Kaplan-Meier analyses were planned for time to event data. Additionally, median survival times and 95% confidence interval should be displayed.

Part B: Time to event data (TTP, OS, PFS, duration of response) were planned to analyse analogously to Part A. For ORR (CR or PR) and DCR (CR, PR or SD) after 2, 4 and 6 months were planned to analyze by absolute and relative frequencies.

Interim analysis:

There was no formal interim analysis planned. After each cohort (up to 10 patients each) in Part A a safety assessment was planned and the next dose strength should be determined. After Part A (up to 20 patients) the safety profile should be assessed. This was an exploratory study, therefore type 1 error inflation and statistical power were not considered after Part A.

20) **Summary – Conclusions[5]:**

8 white and male patients with a mean age of 67.1 years ± 11.2 were enrolled. 6 patients had a baseline ECOG status of 0 and 2 had an ECOG status of 1. The average Child-Pugh Score was 5.3 ± 0.5. 1 patient had a BCLC tumor status B, in 7 patients the BCLC tumor status was assessed as C. Tumor grades were given as 1 patient G1, 5 patients G2, 1 patient G3 and for one patient the assessment was missing.

7 pts completed DKN-01 mono- and 3 pts entered combo therapy. The mean study duration was 110.1 days and ranged 39 to 275 days. The mean treatment duration was 97.6 days ranging from 37 days to 245 days. Monotherapy lasted 61.9 days on average with a minimum of 37 days and a maximum of 85 days. The total mean amount taken of DKN-01 was 1912.5 mg and exposure ranged from 900 mg to 4800 mg.

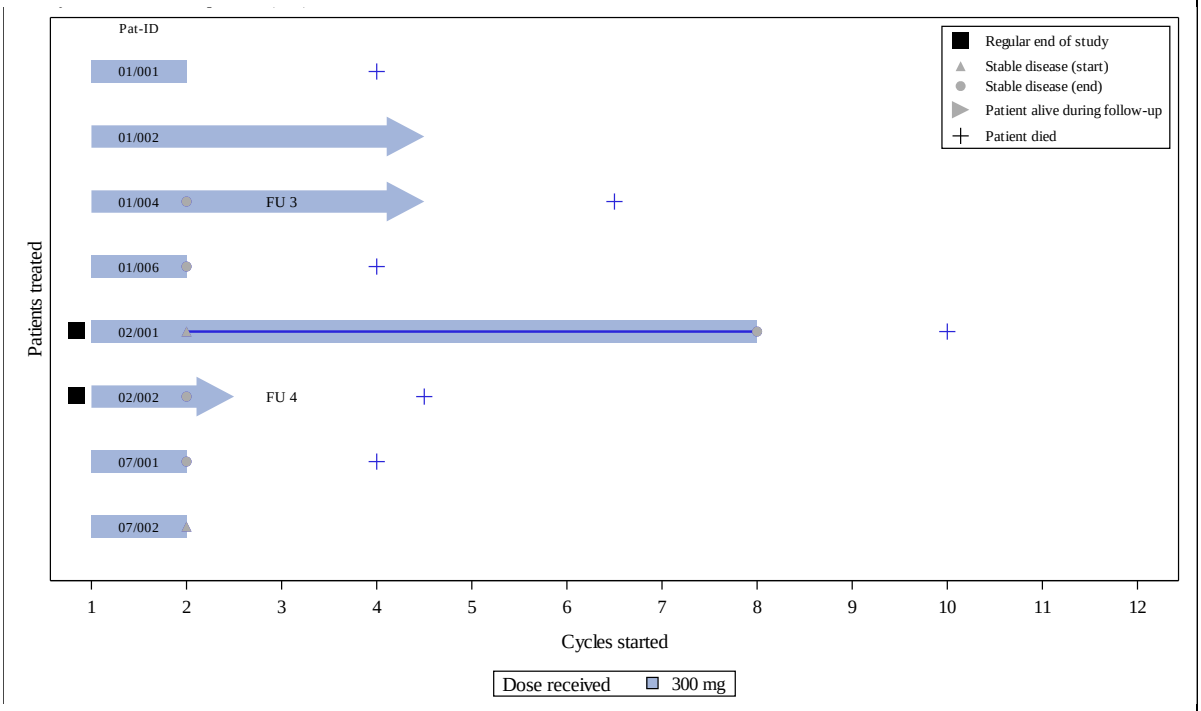
The study was terminated after 8 subjects were enrolled due to difficulty in meeting the study enrollment target and changing treatment paradigms. Given the limited enrollment and all subjects dosed at 300mg, pharmacokinetic analysis was not done

[4] This section should also contain information about the chosen risk management approach, as outlined by ICH E3, section 9.6 (only if the study was approved after June 14th, 2017).

[5] Results should also summarize important deviations from the predefined quality tolerance limits and remedial actions taken (only if the study was approved after June 14th, 2017).

The treatment duration is displayed together with the treatment response in the following figure 1:

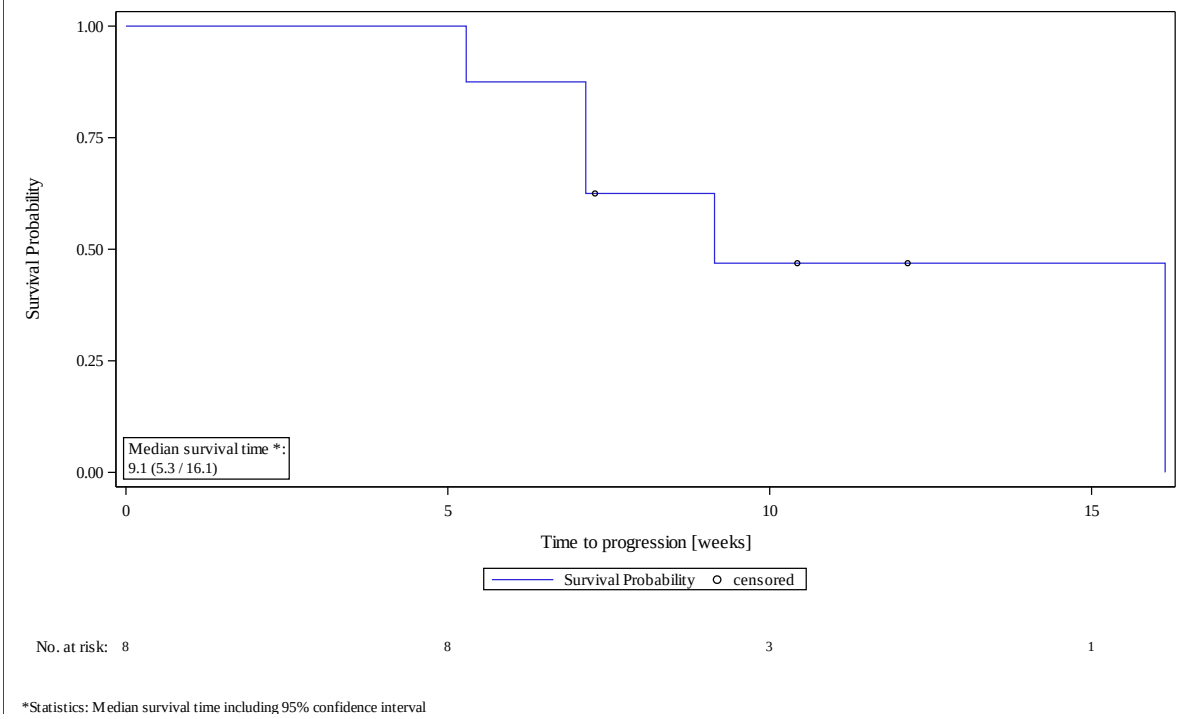
Figure 1: Swimmer Plot of the individual patients



Results:

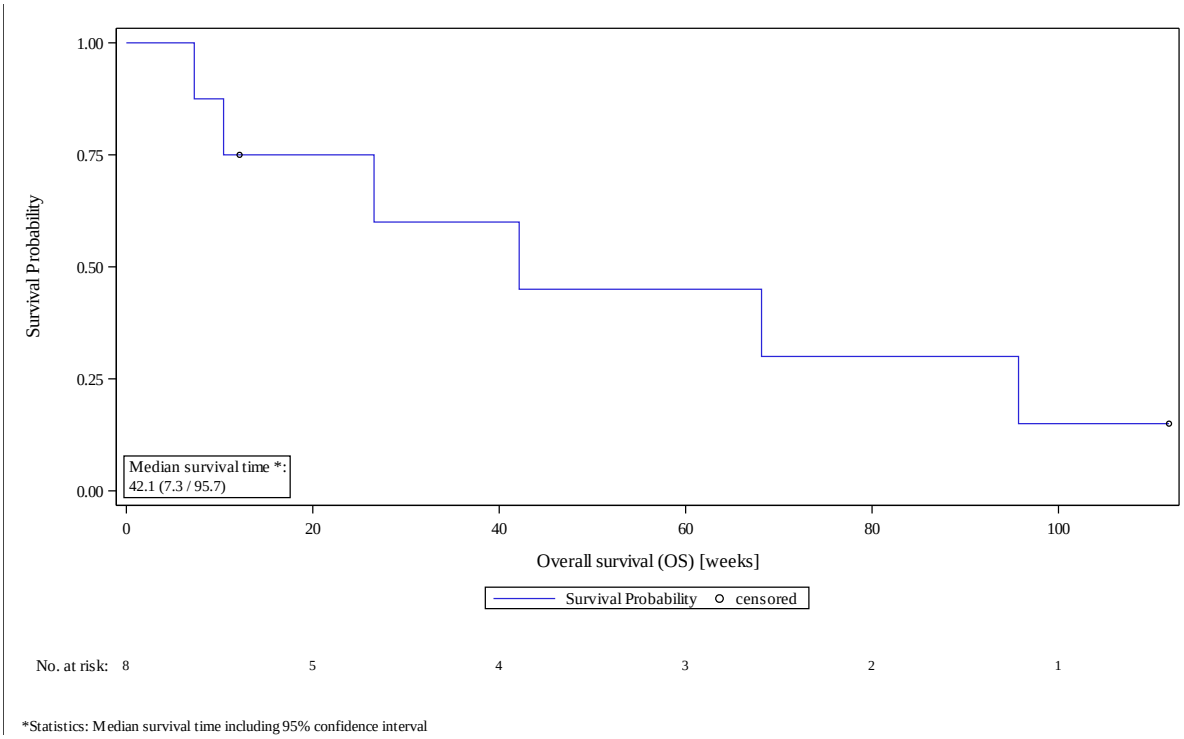
Median TTP1 was 9 weeks with 5 PD and 2 SD following DKN-01 monotherapy. Median PFS was 2 months and median OS was 10.5 months. The time to event data are displayed in the following three figures.

Figure 2: Time to progression 1 (TTP1)



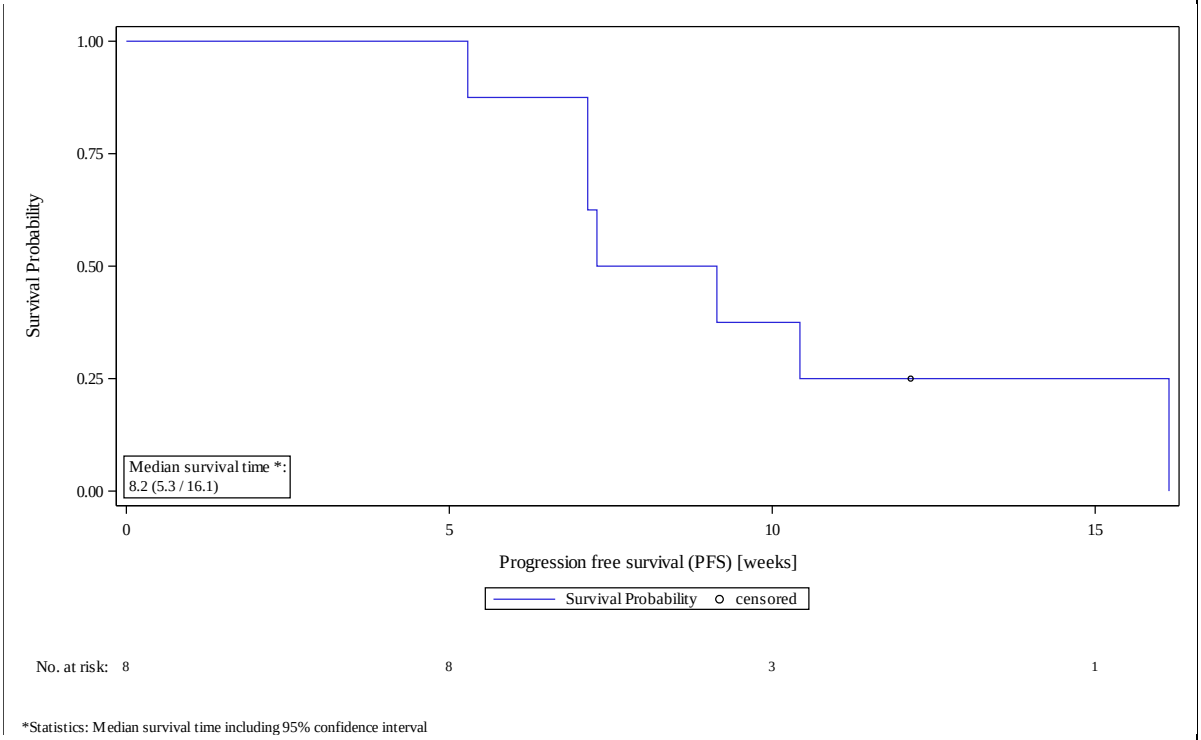
*Statistics: Median survival time including 95% confidence interval

Figure 3: Overall survival



*Statistics: Median survival time including 95% confidence interval

Figure 4: Progression-free survival



*Statistics: Median survival time including 95% confidence interval

Safety results:

All adverse events (AEs) were documented on the appropriate pages of the eCRF and coded with the Medical Dictionary for Regulatory Activities (MedDRA) Version 25.0. The relatedness between each event and the administration of study medication (DKN-01) was judged by the investigators as “related” or “not related” to study medication. Seriousness was defined according to the Seriousness Criteria of Good Clinical Practice Guideline (GCP). Severity assessment was performed in accordance with National Cancer Institute common terminology criteria for adverse events (CTCAE) Version 5.0 to describe the maximum intensity of the adverse event. The following table shows an overview of the reported AEs during mono- or combination therapy and the total number of AEs.

Table 1: Overview of reported AEs*

	Monotherapy		**Combination Therapy**		**Total**	
Patients with	**Patients (N=8)**	**AEs (nAE=48)**	**Patients (N=3)**	**AEs (nAE=25)**	**Patients (N=8)**	**AEs (nAE=73)**
Any AEs	7 (88%)	48 (100%)	3 (100%)	25 (100%)	8 (100%)	73 (100%)
Any severe** AEs	5 (63%)	15 (31%)	1 (33%)	4 (16%)	5 (63%)	19 (26%)
Any related AEs	2 (25%)	3 (6%)	1 (33%)	3 (12%)	3 (38%)	6 (8%)
Any related severe** AEs	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Any SAEs	5 (63%)	15 (31%)	1 (33%)	3 (12%)	5 (63%)	18 (25%)
Any related SAEs	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Any deaths***	2 (25%)	2 (4%)	0 (0%)	0 (0%)	2 (25%)	2 (3%)

Any fatal related AEs	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Any infusion-related AEs	0 (0%)	0 (0%)	1 (33%)	4 (16%)	1 (13%)	4 (5%)
Any infusion-related SAEs	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Any immune-mediated AEs	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Any immune-mediated SAEs	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)

*Treatment emergent only; **Severe AE: CTCAE grade >2; ***Multiple adverse events can lead to the death of a patient.

Adverse Events:

All patients reported at least one AE while under study medication. A total of 73 AEs were reported among which 19 AEs (26%) were graded as severe. During monotherapy 48 AEs were reported (6 per pat.) among which 15 AEs (31%) were graded as severe. During combination therapy 25 AEs were reported (8 per pat.) among which 4 AEs (16%) were graded as severe.

In total there were 4 AEs in 1 patient which were assessed as infusion-related reaction by the investigator.

Table 2: AEs which were assessed as infusion-related reaction by the investigator:

AE Term	**MedDRA preferred term (PT)**	**AE causality assessment DKN-01**	**AE alternative explanation**
Soor	Candida infection	Related	None
Diarrhea	Diarrhoea	Not related	Sorafenib
Diarrhea	Diarrhoea	Related	Sorafenib
Diarrhea	Diarrhoea	Related	Sorafenib

In total the most frequent AE (MedDRA preferred term (PT)) in MedDRA system organ class (SOC) “gastrointestinal disorders” was “diarrhoea“ (5 AEs in 1 pt.), in SOC “infections and infestations” was “spontaneous bacterial peritonitis“(2 AEs in 2 pts.) and in SOC “general disorders and administration site conditions” were “fatigue“ (2 AEs in 2 pts.) and “oedema peripheral (2 AEs in 2 pts.).

During monotherapy the most frequent AE (MedDRA preferred term (PT)) in MedDRA system organ class (SOC) “gastrointestinal disorders” was “abdominal pain“ (4 AEs in 3 pts.), in SOC “infections and infestations” was “spontaneous bacterial peritonitis“ (2 AEs in 2 pts.) and in SOC “general disorders and administration site conditions” was “fatigue“ (2 AEs in 2 pts.).

During combination therapy the most frequent AE (MedDRA preferred term (PT)) in MedDRA system organ class (SOC) “gastrointestinal disorders” was “diarrhoea“ (4 AEs in 1 pt.), in SOC “hepatobiliary disorders” was “hyperbilirubinaemia“ (3 AEs in 1 pt.), in SOC “infections and infestations” were “candida infection“ (1 AE in 1 pt.) and “nasopharyngitis“ (1 AE in 1 pt.) and in SOC “skin and subcutaneous tissue disorders” were “dry skin“ (1 AE in 1 pt.) and “palmar-plantar erythrodysaesthesia syndrome“ (1 AE in 1 pt.).

The following table shows the number of AEs allocated to MedDRA system organ classes (SOCs) during mono- or combination therapy and the total number of AEs.

Table 3: AEs allocated to MedDRA system organ classes (SOCs)

	Monotherapy		**Combination Therapy**		**Total**	
System Organ Class	**Patients (N=8)**	**AEs (nAE=48)**	**Patients (N=3)**	**AEs (nAE=25)**	**Patients (N=8)**	**AEs (nAE=73)**
Infections and infestations	3 (38%)	6 (13%)	1 (33%)	2 (8%)	3 (38%)	8 (11%)

Neoplasms benign, malignant and unspecified (incl cysts and polyps)	1 (13%)	1 (2%)	0 (0%)	0 (0%)	1 (13%)	1 (1%)
Blood and lymphatic system disorders	2 (25%)	2 (4%)	1 (33%)	1 (4%)	2 (25%)	3 (4%)
Endocrine disorders	0 (0%)	0 (0%)	1 (33%)	1 (4%)	1 (13%)	1 (1%)
Metabolism and nutrition disorders	2 (25%)	2 (4%)	1 (33%)	1 (4%)	3 (38%)	3 (4%)
Psychiatric disorders	1 (13%)	1 (2%)	0 (0%)	0 (0%)	1 (13%)	1 (1%)
Nervous system disorders	2 (25%)	2 (4%)	0 (0%)	0 (0%)	2 (25%)	2 (3%)
Vascular disorders	1 (13%)	1 (2%)	1 (33%)	1 (4%)	2 (25%)	2 (3%)
Respiratory, thoracic and mediastinal disorders	1 (13%)	2 (4%)	0 (0%)	0 (0%)	1 (13%)	2 (3%)
Gastrointestinal disorders	5 (63%)	15 (31%)	3 (100%)	11 (44%)	7 (88%)	26 (36%)
Hepatobiliary disorders	1 (13%)	1 (2%)	1 (33%)	3 (12%)	2 (25%)	4 (5%)
Skin and subcutaneous tissue disorders	2 (25%)	3 (6%)	1 (33%)	2 (8%)	2 (25%)	5 (7%)
Musculoskeletal and connective tissue disorders	2 (25%)	2 (4%)	1 (33%)	1 (4%)	3 (38%)	3 (4%)
Renal and urinary disorders	3 (38%)	3 (6%)	1 (33%)	1 (4%)	3 (38%)	4 (5%)
General disorders and administration site conditions	4 (50%)	5 (10%)	1 (33%)	1 (4%)	5 (63%)	6 (8%)
Investigations	1 (13%)	1 (2%)	0 (0%)	0 (0%)	1 (13%)	1 (1%)
Injury, poisoning and procedural complications	1 (13%)	1 (2%)	0 (0%)	0 (0%)	1 (13%)	1 (1%)

Adverse Events considered as related to study medication (ADRs):

In total there were 6 (8%, 0.8 per pat.) AEs in 3 patients where a positive causal relationship was assessed by the investigator between the occurrence of the AE and the administration of study medication. During monotherapy in 3 (6%, 0.4 per pat.) of all AEs a positive causal relationship was assessed by the investigator between the occurrence of the AE and the administration of study medication. The following ADRs occurred (MedDRA preferred terms (PTs)): “nausea” (1 ADR in 1 patient), “pruritus“ (1 ADR in 1 patient) and “fatigue” (1 ADR in 1 patient). During combination therapy in 3 (12%, 1 per pat.) of all AEs a positive causal relationship was assessed by the investigator between the occurrence of the AE and the administration of study medication. The following ADRs occurred (MedDRA preferred terms (PTs)): “candida infection” (1 ADR in 1 patient) and “diarrhoea” (2 ADRs in 1 patient).

Severity of Adverse Events:

For severity analysis CTCAE grade < 2 was classified as mild, CTCAE grade 2 as moderate and CTCAE grade >2 as severe. 32 (44%) of all AEs were judged as mild, 22 (30%) as moderate and 19 (26%) as severe. None of the severe AEs was assessed as related to study medication. During monotherapy 16 (33%) of all AEs were judged as mild, 17 (35%) as moderate and 15 (31%) as severe, during combination therapy 16 (64%) of all AEs were judged as mild, 5 (20%) as moderate and 4 (16%) as severe.

Seriousness of Adverse Events:

In summary, 18 (25%, 2 per pat.) AEs were judged as serious according to the definition in the study protocol and documented in the study database. 5 (63%) patients reported at least one serious adverse event (SAE) while under study medication.

The MedDRA system organ class (SOC) with most SAEs was “gastrointestinal disorders” (7 SAEs in 4 pts.). The following SAEs (MedDRA preferred terms (PTs)) were reported in this SOC: “abdominal pain” (2 SAEs in 2 pts.), “gastric varices haemorrhage” (2 SAEs in 1 pt.) and “gastrointestinal haemorrhage (3 SAEs in 2 pts.).

None of the serious AEs was assessed as related to study medication (SAR) and no suspected unexpected serious adverse reaction (SUSAR) had to be reported to the competent authority, ethics committee and all investigators. No SAE was evaluated as dose-limiting toxicity (DLT) regarding DKN-01 by the coordinating investigator. The following table shows the number of SAEs allocated to MedDRA system organ classes (SOCs) during mono- or combination therapy and the total number of AEs.

Table 4: SAEs allocated to MedDRA system organ classes (SOCs)

	Monotherapy		**Combination Therapy**		**Total**	
System Organ Class	**Patients (N=8)**	**SAEs (nSAE=15)**	**Patients (N=3)**	**SAEs (nSAE=3)**	**Patients (N=8)**	**SAEs (nSAE=18)**
Infections and infestations	2 (25%)	3 (20%)	0 (0%)	0 (0%)	2 (25%)	3 (17%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	1 (13%)	1 (7%)	0 (0%)	0 (0%)	1 (13%)	1 (6%)
Blood and lymphatic system disorders	2 (25%)	2 (13%)	1 (33%)	1 (33%)	2 (25%)	3 (17%)
Gastrointestinal disorders	4 (50%)	5 (33%)	1 (33%)	2 (67%)	4 (50%)	7 (39%)
Hepatobiliary disorders	1 (13%)	1 (7%)	0 (0%)	0 (0%)	1 (13%)	1 (6%)
Renal and urinary disorders	2 (25%)	2 (13%)	0 (0%)	0 (0%)	2 (25%)	2 (11%)
Injury, poisoning and procedural complications	1 (13%)	1 (7%)	0 (0%)	0 (0%)	1 (13%)	1 (6%)

SAEs with fatal outcome:

In this clinical trial two SAEs with fatal outcome were reported during monotherapy. One patient died due to progressive disease of his underlying tumor disease (MedDRA preferred term (PT): “malignant neoplasm progression”) and one patient fell down a stairway by accident with fatal fracture of cervical spine (MedDRA preferred term (PT): “cervical vertebral fracture”).

Summary concerning safety:

In summary, in this clinical trial 9 (2 severe) adverse events (AEs) per patient, 2 serious adverse events (SAEs) per patient and no serious adverse drug reaction (SAR) were reported to the sponsor. During monotherapy 6 (2 severe) adverse events (AEs) per patient, 2 serious adverse events (SAEs) per patient and no serious adverse drug reaction (SAR) were reported to the sponsor. During combination therapy 8 (1 severe) adverse events (AEs) per patient, 1 serious adverse events (SAEs) per patient and no serious adverse drug reaction (SAR) were reported to the sponsor.

In total the most frequent AE (MedDRA preferred term (PT)) was “diarrhoea“ (5 AEs in 1 pt.) and the most frequent related AE (MedDRA preferred term (PT)) was “diarrhoea“ (2 AEs in 1 pt.). During monotherapy the most frequent AE (MedDRA preferred term (PT)) was “abdominal pain“ (4 AEs in 3 pts.), there was no difference in the frequency of the related AEs (MedDRA preferred term (PT)) “nausea“ (1 AE in 1 pt.), “pruritus“ (1 AE in 1 pt.) and “fatigue“ (1 AE in 1 pt.). During combination therapy the most frequent AE (MedDRA preferred term (PT)) was “diarrhoea“ (4 AEs in 1 pt.) and the most frequent related AE (MedDRA preferred term (PT)) was “diarrhoea“ (2 AEs in 1 pt.).

Report Synopsis of Study Dial-1

EudraCT-Nr.: 2017-002468-41

Vorlage-Nr.: 3287

Conclusion:

DKN-01 was safely administered and showed a manageable safety profile with and without sorafenib treatment. As monotherapy it had limited anti-tumor effects.

I hereby confirm, that the data in the results report were collected properly and are correct.

21) **Date of the report:** 01,12,2022

Print Name: Professor Dr, med Jens Marquardt (LKP)

Signature: