Nab-Paclitaxel (Abraxane®) and Gemcitabine as first line therapy in patients with **cho**langiocarcinoma ineligible for cisplatin-based chemotherapy – a pilot study

The NACHO trial (GEMNABCCC-001)

An interventional, prospective, non-randomized, controlled, open label, pilot study testing Nab-Paclitaxel (Abraxane®) and Gemcitabine as first line therapy in patients with cholangiocarcinoma ineligible for cisplatin-based chemotherapy

Name of the investigational Drug
Nab-Paclitaxel (Abraxane®)

Indication
unresecable, metastatic or recurrent cholangiocarcinoma (intrahepatic cholangiocellular carcinoma, bile duct cancer, gall bladder carcinoma)

Clinical pilot trial

Short Title / Acronym: NACHO

EudraCT Number: 2014-004981-52

Study start date – study end date
First patient in: 06-Dec-2016 – Last patient out: 02-Oct-2019

Clinical Study Report

Sponsor of the Clinical Trial:

University of Duisburg-Essen
Hufelandstraße 55
D-45122 Essen, Germany
Phone: 0201 / 723-1791
Email: stefan.kasper-virchow@uk-essen.de

National Coordinating Investigator / Investigator:

Prof. Dr. med. Stefan Kasper-Virchow
University of Duisburg-Essen Medical School
West German Cancer Center
Hufelandstraße 55
D-45122 Essen, Germany
Phone: 0201 / 723-1791
Fax: 0201 / 723-59 24
Email: stefan.kasper-virchow@uk-essen.de

Version 1.0, dated 27Jul-2022

Synopsis

Sponsor:
University of Duisburg-Essen, Hufelandstraße 55, D-45122 Essen, Germany
represented by Prof. Dr. Stefan Kasper-Virchow
Phone: 0201 / 723-3449
Fax: 0201 / 723-6276
Email: stefan.kasper-virchow@uk-essen.de

Investigational medicinal product: Abraxane®

Drug substance: nab-paclitaxel

Registration:
EudraCT-No.: 2014-004981-52

Study title:
Nab-Paclitaxel (Abraxane®) and Gemcitabine as first line therapy in patients with cholangiocarcinoma ineligible for cisplatin-based chemotherapy – a pilot study - The NACHO trial (GEMNABCCC-001)

National Coordinating Investigator:
Prof. Dr. med. Stefan Kasper-Virchow
University of Duisburg-Essen Medical School
West German Cancer Center
Hufelandstraße 55
D-45122 Essen, Germany
Phone: 0201 / 723-3449
Fax: 0201 / 723-6276
Email: stefan.kasper-virchow@uk-essen.de

Study sites: 1 active site in Germany

First patient in: 06-Dec-2016 **Last patient out:** 02-Oct-2019	**Phase:** II

Study objective(s):
Primary objective: Overall response rate (ORR) using RECIST Criteria V. 1.1
Secondary objectives:

- Disease control rate (DCR) (complete remission, partial remission and stable disease for at least 8 weeks) (estimated 80%)*
- Progression free survival (PFS) (estimated 8 months)*
- PFS rate at 6 months (estimated 60%)*
- Overall survival (OS) (estimated 12 months)*
- Serological response (decrease in CA19-9 levels)
- Toxicity/safety

*based on the combination cisplatin/gemcitabine (Valle et al., 2010)

Trial design:
Open, prospective, phase II pilot study

Methods:
This study evaluated the efficacy and safety of Gemcitabine/nab-Paclitaxel in first-line therapy of patients with cholangiocarcinoma ineligible for Cisplatin-based therapy. Upon obtaining signed informed consent, screening evaluations were performed to confirm eligibility and to obtain baseline safety data. Enrolled patients with histologically or cytologically documented diagnosis of cholangiocellular carcinoma, bile duct cancer or gall bladder carcinoma, who had unresecable, metastatic or recurrent disease and who were ineligible for cisplatin received a chemotherapy witrh gemcitabine and nab-paclitaxel. Treatment was

continued until progressive disease was documented or unacceptable toxicity occurred. Response was assessed on CT- or MRI-scans every 8 weeks until progression of disease. Adverse events were categorized in regard to their relationship to treatment with the chemotherapeutic compounds (using National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) grading (version 4.0), severity, action taken, and outcome.

Number of patients (planned and analyzed)

Planned: 10 patients

Analyzed:

- 10 patients in ITT and safety set (received at least one dose of any study treatment)

Diagnosis and key inclusion criteria:

- signed informed consent before start of specific protocol procedure
- age > 18 years
- histologically or cytologically documented diagnosis of cholangiocellular carcinoma, bile duct cancer or gall bladder carcinoma
- presence of at least one measurable site of disease following RECIST 1.1 criteria
- unresecable, metastatic or recurrent disease
- ECOG performance 0 or 1
- life expectancy of at least 3 months
- any contraindication for Cisplatin, i.e. renal impairment (creatinine clearance < 60 ml/min), impaired hearing, increased risk or history for thromboembolic events, intolerance of extensive hydration, left ventricular ejection fraction (LVEF) < 45%
- adequate bone marrow, liver and renal function as assessed by the following laboratory requirements to be conducted within 7 days prior to screening
- absolute neutrophil count (ANC) ≥ 1500/µl
- platelet count ≥ 100,000/µl
- total bilirubin < 3 x ULN and sufficient biliary drainage
- ALT and AST < 3 x ULN, < 5 x ULN if liver metastasis present
- PT-INR/PTT < 1.5 x ULN, patients therapeutically anticoagulated with NMH, heparin or NOACs (dabigatran, rivaroxaban, abixaban) are allowed to participate, patients anticoagulated with phenoprocoumon or warfarin should be switched to NMH, heparin or NOACs
- creatinine clearance ≥ 30ml/min and serum creatinine ≤ 2.5 x ULN
- confirmed menopause, negative pregnancy test within 7 days of the start of treatment and willingness to use highly effective methods of contraception
- willingness and able to comply with the protocol for the duration of the study

Key exclusion criteria:

- metastatic, advanced or recurrent disease; adjuvant/additive chemotherapy or radiotherapy after resection is allowed if therapy free intervall is at least 4 months; concomitant small volume palliative radiotherapy of bone metastases are allowed
- investigational drug therapy during or within 4 weeks of study entry
- major surgery within 4 weeks of starting therapy within this study
- symptomatic brain metastasis
- clincially significant cardiovascular disease (incl. Myocardial infarction, unstable angina, symptomatic congestive heart failure, serious uncontrolled cardiac arrhythmia) 6 months before enrollment
- active clinically serious infections (> grade 2 NCI-CTC version 4.0)
- history of interstitial lung disease
- liver cirrhosis child-pugh score > 8
- history of HIV infection or chronic hepatitis B or C
- pre-exisiting neuropathy > grade 1 (NCI-CTC version 4.0)
- patients with evidence of bleeding diathesis

- patients with second primary cancer within 5 years, exept adequately treated basal skin cancer or carcinoma in-situ of the cervix or bladder, or low/intermediate risk prostate cancer (Gleason score ≤ 7) with normal PSA levels
- any condition that could jeopardize the safety of the patient and their compliance of the study
- breast-feeding patients
- substance abuse, medical, psychological or social conditions that may interfere with the participation in the study

Investigational medicinal product (dosage, method of administration):

For Patients with normal bilirubin values (≤ 1.5x ULN):

Gemcitabine (commercially available)

1000mg/m² i.v. day 1, 8, 15

Nab-Paclitaxel (Abraxane®) (supplied free of charge by the manufacturer)

125mg/m² i.v. day 1, 8, 15

repeat the cycle at day 28, until disease progression

For Patients with elevated bilirubin values >1.5-3x ULN):

Gemcitabine (commercially available)

800mg/m² i.v. day 1, 8, 15

Nab-Paclitaxel (Abraxane®) (supplied free of charge by the manufacturer)

100mg/m² i.v. day 1, 8, 15

dose escalation in cycle 2, if cycle 1 was tolerated without significant toxicities (grade 3 or 4) to

Gemcitabine (commercially available)

1000mg/m² i.v. day 1, 8, 15

Nab-Paclitaxel (Abraxane®) (supplied free of charge by the manufacturer)

125mg/m² i.v. day 1, 8, 15

repeat the cycle at day 28, until disease progression

Duration of treatment:
Study treatment was to be given until progression or unacceptable toxicities or patient's wish, whichever occurred first.

Reference product (dosage, method of administration, batch number): Not applicable

First reference drug: Not applicable
Second reference drug: Not applicable

Unblinding: Not applicable

Efficacy evaluation:
Efficacy was evaluated according to RECIST 1.1 criteria. The primary objective was the overall response rate [= patients with either complete response (CR) or partial response (PR) as best response divided by the number of patients eligible for the ITT].

Further efficacy objectives were safety, the disease control rate, progression-free survival (PFS), PFS rate at 6 months, serological response, overall survival (OS) and quality of life.

Safety evaluation:

All adverse events either related or not related to study treatment were documented. Toxicities were defined according to the NCI-CTC-Toxicity Criteria version 4.0.

Statistical methods:

This is an explorative pilot trial with a cohort of 10 patients. So far no data for the efficacy of the combination of Gemcitabine and nab-Paclitaxel in CCA is available. In addition this study is conducted in a patient population with comorbidities and not eligible for the standard chemotherapy for this disease. This population is usually underrepresented in clinical trials. The major reason for conducting this pilot trial is to determine initial data in order to perform a sample size calculation for an expansion phase (single arm, or a randomized phase II trial) (Lancaster GA *et al.*, 2004). Usually 10 participants or 10% of the final study size are included in an explorative pilot trial (Nieswiadomy, 2002; Lackey and Wingate, 1998; Hully et al., 2001).

All parameters will be evaluated in an explorative or descriptive manner, providing means, medians, ranges, standard deviations and/or confidence intervals. If any p values are calculated (e.g. in subgroup comparisons), they are considered to be descriptive and will be presented explicitly without referring to hypotheses or a significance level. Usually, no error adjustment for multiple testing will be performed. Thus the p values will reflect the comparison-wise error and not the experiment-wise error. All p values will be two-sided if not stated otherwise. The statistical methods described in this section are suited for the data and distributions usually expected in this type of trials. The suitability will be checked after data entry. If necessary, the statistical method will be modified accordingly, with critical discussion of the original and modified results. Overall response rate (primary endpoint), median PFS and OS, toxicity and other event rates at pre- specified time points are calculated, providing confidence intervals. In case of comparison between patient groups, these rates will be analyzed by Fishers exact test, χ^2 test. Event related data like PFS or OS will be estimated using Kaplan Meier curves (Kaplan and Meier, 1958). Multivariate analyses will eventually be performed by suitable regression models (logistic regression, proportional hazard regression model) (Cox 1972).

Summary of results:

Efficacy:

Altogether 10 patients were enrolled into the trial and received at least one cycle of chemotherapy (ITT-population), In total 4 of the ITT set had CR or PR as best response; this amounted to an ORR of 40%.
DCR (CR+PR+SD) was 80%.
Median PFS was 5.7 months.
PFS rate at 6 months was 30%
Median OS amounted to 7.8 months.

Tolerability:

In total 153 AEs were reported in 10 patients; of these, 84 AEs were related to study medication. 120 AEs were of grade 1-2, 20 AEs were of grade 3-4 and 13 Aes were not assessed for grade. There was no grade 5 AE documented. Most of AEs belonged to System Organ Class (SOC) ‘Blood and lymphatic system disorders’, ‘skin and subcutaneous tissue disorders’, ‘gastrointestinal disorders’ and ‘General disorders and administration site conditions’. Most frequent reported preferred terms (PT) were ‘Peripheral sensory neuropathy’, ‘Asthenic conditions’, ‘Diarrhoea’ and ‘Thrombocytopenia’.

Thirteen AEs were assessed as serious by the investigator in 6 patients, of which 6 were related to study medication. Six and four SAEs belonged to SOC ‘General disorders gastrointestinal disorders’ and ‘infections and infestation`, respectively. All SAEs recovered.

No SUSARs were observed.

Conclusion(s):

The Nacho-trial suggests that the combination chemotherapy with gemcitabine and nab-paclitaxel is safe and effective in patients, which are ineligible for the standard combination chemotherapy with cisplatin and gemcitabine and could be an alternative treatment regime in the future or warrant a larger randomized phase II trial in these frail patient population.

Date of report: 27-Jul-2022

Table of contents

1 List of Acronyms & Abbreviations and Definitions

AE	Adverse Event
AMG	German Medicinal Products Act
BfArm	Bundesinstitut für Arzneimittel und Medizinprodukte
BSA	Body surface area
BTC	Biliary Tract cancer
CCA	Cholangiocarcinoma
CR	Complete Response
CRF	Case Report Form
CRO	Contract Research Organisation
d	Day
DCR	Disease control rate
DMP	Data Management Plan
DNA	Deoxyribonucleic Acid
ECG	Electrocardiography
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic Case Report Form
EORTC	European Organization for Research and Treatment of Cancer
f	female
h	Hour
ß-hCG	Beta-Human Chorionic Gonadotropin
ICH GCP	International Conference on Harmonisation - Good Clinical Practice
ICD-10	International Statistical Classification of Diseases and Related Health Problems
IEC	Independent Ethics Committee
INR	International Normalized Ratio
IRB	Institutional Review Board
ITT	Intent-to-treat (population)
iv	Intravenous
LKP	National Coordinating Investigator
m	male
MedDRA	Medical Dictionary for Drug Regulatory Affairs
na	Not available
n.d.	Not determined
n.e.	Not evaluated
NEC	Not elsewhere classified
NCI-CTC	National Cancer Institute Common Terminology Criteria
NOS	Not otherwise specified
NR	Not related
ORR	Overall Response Rate
PD	Progressive disease
PR	Partial Response
PT	Preferred Term
PTT	Partial Thromboplastin Time
R	Related
QLQ	Quality of Life Questionnaire
RNA	Ribonucleic Acid
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SEM	Standard Error of the Mean
SD	Stable Disease

SGOT	Serum Glutamate Oxaloacetic Transaminase
SGPT	Serum Glutamate-Pyruvate Transaminase
SmPC	Summary of Product Characteristics
SOC	System Organ Class
SP	Safety Population
SUSAR	Suspected Unexpected Serious Adverse Reaction
TRAE	Treatment related AE
ULN	Upper limit norm

2 Ethics

2.1 Independent Ethics Committee (IEC) or Institutional Review Board (IRB)

Before the beginning of the clinical trial, approval of the responsible Independent Ethics Committee (IEC) was obtained. The responsible IEC of the principle investigator was the ethics committee of the University of Essen. The study was approved on 28-Sep-2016 (16-7068-AF).

2.2 Ethical Conduct of the Study

The regulatory basis of the conduct of this study consisted of the Declaration of Helsinki (in its current version), the AMG [German Medicinal Products Act], in particular Sections 40-42 in the current versions, the guidelines of Good Clinical Practice (ICH-GCP: International Conference on Harmonisation –Good Clinical Practice) valid since 17-Jan-1997, and the GCP-regulation of 09-Aug-2004 (last change of 15-Mar-2006).

In accordance with the AMG, the sponsor had taken out insurance for all subjects who gave consent to participation in the clinical trial.

2.3 Patient Information and Consent

Patients' written informed consent was a prerequisite before entering the study (i.e., prior to any examinations and procedures exclusively associated with the selection for the study or any study-specific data was recorded on study-specific forms).
Adequate information was given to the patient by the investigator before informed consent was obtained. A patient information sheet in the local language was provided for the purpose of obtaining informed consent. The patient information sheet was revised whenever important new information became available that could be relevant to the consent of patients.
In addition to this written information, the investigator or designate informed the patient verbally about the purpose and conduct of the study. In doing so, the wording used was chosen so that the information could be fully and readily understood by laypersons. The patient was given sufficient time and opportunity to decide on participation and to clarify any outstanding questions prior to signing the informed consent.
The written informed consent of the patient to participate in the clinical study had to be signed and personally dated by the patient and by the investigator/person designated by the investigator to conduct the informed consent discussion. Patients were also asked to give consent to additional analysis of tumor material. This approval was not a precondition for participation in the study.
Provision of consent was confirmed both in the patient file and in the case report form (CRF) by the investigator. The original of the signed and dated informed consent form remained at the investigator's site file and had to be safely archived by the investigator so that the forms could be retrieved at any time for monitoring, auditing and inspection purposes. The patient received a copy of the signed and dated informed consent.

A sample Patient Information Sheet and Informed Consent Form is provided in the Appendix 13.1.4.

2.4 Funding

This study was in parts funded by Bristol-Myers Squibb (formely Celgene GmbH), which also provided nab-paclitaxel (Abraxane®) free of charge.

3 Investigators and Study Administrative Structure

This was an investigator initiated trial. Sponsor was the University of Duisburg-Essen, Germany, represented by Prof. Dr. med. Stefan Kasper-Virchow from the University Hospital Essen, West German Cancer Center who also was the Coordinating Investigator.
Blood samples and paraffin-embedded tumor samples were collected and sent to the central laboratory of the University Hospital Essen.
Statistical analysis was performed by Prof. Dr. Stefan Kasper-Virchow, University Hospital Essen, Clinic for Internal Medicine (Tumor Research). The Statistical Analysis Plan was prepared by Prof. Dr. Stefan Kasper-Virchow.
Prof. Stefan Kasper-Virchow was responsible for the creation of the CRF (CRF) as well as for creation of the clinical study report. In addition, Prof. Dr. Stefan Kasper-Virchow and Gabriele Linden performed the submission to the higher competent authority (BfArm) and to the responsible and local ethics committees.

4 Introduction

The overall incidence of adenocarcinomas of the biliary tract, including carcinoma of the gallbladder, carcinoma of the extrahepatic bile duct and intrahepatic cholangiocellular carcinoma (referred to as CCA in the rest of the text) is less than 3/100,000 in caucasian (Razumilava N, Gores GJ 2014). Epidemiologic studies suggest its incidence is increasing in Western countries during the last decades (Razumilava N, Gores GJ 2014). The only curative option for patients with CCA is surgical resection but unfortunately R0 resection rates are less than 30% because tumors are frequently diagnosed in advanced stages due to absent tumor related symptoms (Razumilava N, Gores GJ 2014). Even after curative intended resection five year survival rate amounts to only 5 to 10% (Kubicka S, 2004). In locally advanced or metastatic disease median overall survival time is not longer than 12 months (Valle J *et al.*, 2010 and 2014.

4.1 Systemic therapy in advanced CCA

Chemotherapy in locally advanced or metastastic CCA improve quality of life and prolongs survival compared to best supportive care (Glimelius B *et al.*, 1996). Objective response rates in studies with single-drug fluoropyrimdine or Gemcitabine based chemotherapy range between 7-38% (Hezel AF *et al.*, 2008). An improvement of overall survival have been observed in a randomized phase III study (ABC-02) with a chemotherapy combination of Cisplatin and Gemcitabine (CisGem) (n=206) compared to Gemcitabine mono-chemotherapy (n=204). Objective response rate was improved from 16% to 26%, disease control rate (CR+PR+SD) was improved from 72% to 81% by the combination therapy, while PFS was prolonged significantly from a median of 5 to 8 months ($p<0.001$). Median overall survival was 8.1 month in the monotherapy arm versus 11.7 month in the combination arm ($p < 0.0001$) (Valle J *et al.*, 2010). A second randomized phase III trial evaluating the addition of Cisplatin to Gemcitabine mainly conducted in Japan showed similar results (Okusaka T *et al.*, 2010; Valle J *et al.*, 2014. As a consequence of these studies the combination of Cisplatin (25 mg/m^2 d1,8) and Gemcitabine (1000 mg/m^2 d1,8) every three weeks should be considered as the standard first line chemotherapy for patients with irresectable CCA in a good performance score without comorbidities.

4.2 Study Rationale

Based on two randomized phase III trials the combination chermotherapy with Gemcitabine and Cisplatin has become the standard first line therapy in advanced CCA. However, a substantial fraction of patients suffer from comorbidities, which preclude Cisplatin-based chemotherapy. Amongst others these include impaired renal function, high risk for thrombembolic complications, or impaired cardiac function. Currently, such patients are offered Gemcitabine monotherapy, which is clearly inferior to more active chemotherapy combinations (Valle J *et al.*, 2014).

Cholangiocarcinomas have similar biologic characteristics as pancreatic cancer, such as distinct tumor-stroma interaction, hypoxic microenvironment, intratumoral inflammation and early metastatic dissemination (Sato Y *et al.*, 2014; Abraham SC *et al.*, 2003; Rizvi S *et al.*, 2013 and 2014; Okuda K *et al.*, 2002; Gandou C *et al.*, 2013). In addition clinical courses and prognosis of patients with CCA are highly similar to patients with pancreatic cancer.
The combination of Gemcitabine and nab-Paclitaxel was shown to be highly effective in advanced pancreatic cancer patients resulting in improved response rates, prolonged progression-free and overall survival as compared to Gemcitabine monotherapy (von Hoff DD *et al.*, 2013). Gemcitabine/nab-Paclitaxel generally is well tolerated also by comorbid patients. In particular, extensive hydration regimens are not required. This combination was approved by the FDA and the EMA as one first line therapeutic option for patients with advanced pancreatic cancers.
As a consequence of the similar biologic characteristics Gemcitabine/nab-Paclitaxel should also be an effective combination in advanced CCA.

5 Study Objectives

The primary objective was the response rate which was determined according to the RECIST Criteria V. 1.1.

Secondary Objectives were

- Disease control rate (DCR) (complete remission, partial remission and stable disease for 8 weeks) (estimated 80%)*
- Progression free survival (PFS) (estimated 8 months)*
- PFS rate at 6 months (estimated 60%)*
- Overall survival (OS) (estimated 12 months)*
- Serological response (decrease in CA19-9 levels)
- Toxicity/safety

*(based on combination cisplatin/gemcitabine (Valle et al., 2010))

6 Investigational Plan

6.1 Overall Study Plan / Study Design

This was an interventional, prospective, non-randomized, controlled, open label, pilot study testing Nab-Paclitaxel (Abraxane®) and Gemcitabine as first line therapy in patients with cholangiocarcinoma ineligible for cisplatin-based chemotherapy.
It was planned to enroll 10 evaluable patients, who fulfilled the inclusion and exclusion criteria. Altogether 10 patients were registered in one German study site. The second planned study center was not initiated.

After registration into the clinical trial patients with normal bilirubin values (≤1.5 ULN) received gemcitabin 1000 mg/m² and nab-paclitaxel (Abraxane®) 125mg/m² as an intravenous infusion on day 1, 8 and 15 ever 4 weeks. Infusion time for gemcitabine and for nab-paclitaxel was 30 minutes. Gemcitabine was infused directly after the administration of nab-paclitaxel. Patients with elevated bilirubin levely (>1.5-3x ULN) received gemcitabin 800 mg/m² and nab-paclitaxel (Abraxane®) 100mg/m² as an intravenous infusion on day 1, 8 and 15 every 4 weeks in the first cycle. If this dose was tolerated without significant side-effects (grade 3 or 4), a dose escalation to gemcitabine 1000mg/m² day 1,8 and 15 and nab-paclitaxel 125mg/m² day 1, 8 and 15 was recommended in the second cycle.

Treatment schedule (q4w):

Drug	Dose	Infusion time	Day (d)
Bilirubin ≤1.5 ULN			
Nab-Paclitaxel (Abraxane®)	125 mg/m² BSA iv	30min	d 1, d 8, d15
Gemcitabine	1000 mg/m² BSA iv	30min	
Bilirubin >1.5-3 ULN			
Nab-Paclitaxel (Abraxane®)	100 mg/m² BSA iv	30min	d 1, d 8, d15, in first cycle; dose escalation recommendet from 2nd cycle on
Gemcitabine	800 mg/m² BSA iv	30min	

All medications were prepared for infusion according to the respective summaries of product characteristics (SmPC).
Pre-treatment with a corticosteroid (at a dose equivalent to ≥8 mg dexamethasone intravenous) and a 5-HT3 antagonist (intravenous, at standard dosage) was also recommended before all infusions of chemotherapy.

If treatment with chemotherapy was delayed or interrupted, the decision to restart chemotherapy administration was based on the neutrophil and platelet counts and the severity of non-haematological toxic effects observed on the day treatment was to be restarted. The chemotherapy should be given only when:

- The neutrophil count is ≥1,500/mm³.
- The platelet count is ≥100,000/mm³.
- Chemotherapy-related toxicities recovered to grade ≤2.
- No ongoing requirement for anti-diarrheic treatment
- Bilirubin ≤ 1.5 x ULN (total bilirubin < 3 x ULN if tumor related)
- ALT and AST < 3 x ULN, (< 5 x ULN if liver metastasis present)
- No persisting cardiac toxicity
- Creatinine clearance ≥ 30 ml/min and serum creatinine ≤ 2.5 x ULN
- No uncontrolled infection
- No treatment delay of more than 3 weeks

Doses were reduced for hematologic and other toxicities. Dose adjustments has to be made according to the system showing the greatest degree of toxicity. Toxicities were graded using the NCI CTCAE Version 3.0.
Two dose modifications were permitted according to the criteria below. If a toxicity requiring dose modification occured following the second dose reduction of either drug, further treatment was discontinued.

General dose modification

Dose Level	Nab-Paclitaxel (mg/m²)[a]	Gemcitabine (mg/m²)[a]
Study dose	125	1000
-1	100	800
-2[b]	75	600

a. Dose reductions may or may not be concomitant. Please refer to specific recommendations outlined below regarding dose reductions

b. A maximum of 2 dose level reductions is allowed.

General dose modification for patients starting at reduced dose

Dose Level	Nab-Paclitaxel (mg/m²)[a]	Gemcitabine (mg/m²)[a]
Study dose	100	800
-1[b]	75	600

a. Dose reductions may or may not be concomitant. Please refer to specific recommendations outlined below regarding dose reductions

b. A maximum of 1 dose level reductions is allowed.

Dose modifications for hematologic toxicity on day 1 of each cycle and within a cycle

Cycle Day	ANC (x 10^9/l)		Platelets (x 10^9/l)	Nab-Paclitaxel/Gemcitabine
Day 1	< 1,5	or	< 100	Delay doses until recovery
Day 8	0,5 to < 1,0	or	50 to < 75	Reduce one dose level
	< 0,5	or	< 50	Withhold doses
Day 15: If day 8 was reduced or given without dose modification:				
	0,5 to < 1,0	or	50 to < 75	Reduce one dose level from day 8
	< 0,5	or	< 50	Withhold doses
Day 15: If day 8 was withheld:				
	≥ 1,0	and	≥ 75	Reduce one dose level from day 1
	0,5 to < 1,0	or	50 to < 75	Reduce two dose levels from day 1
	< 0,5	or	< 50	Withhold doses

Febrile neutropenia:

Febrile neutropenia	
Febrile neutropenia (grade 3 or 4)[a,b]	Discontinue nab-Paclitaxel and Gemcitabine until fever resolves and ANC ≥ 1500 x 10^9/l, resume at next lower dose level and continue throughout the rest of treatment

a. For grade 4 neutropenia within a treatment cycle in the absence of fever (i.e. day 21). Nab-Paclitaxel and Gemcitabine dosing is not to be interrupted and G-CSF may be initiated as per institutional guidelines. Patients not experiencing resolution of neutropenia within 21 days, despite uninterrupted G-CSF treatment, will be discontinued from the study

b. Febrile patients (regardless of neutrophil count) should not receive chemotherapy. A full diagnostic work-up for septicemia should be performed and broad-spectrum antibiotics should be applied. Patients with persisting fever after 2 weeks, despite continuous antibiotic treatment, will be taken off the study. Patients with febrile neutropenia can also receive G-CSF, in addition to antibiotic treatment, following current institutional guidelines and other specific guidelines (e.g. ASCO, ESMO). In all cases, blood counts must have returned to baseline levels before resuming chemotherapy treatment.

Non-hematologic toxicity

Dose modifications for non-hematologic toxicity on day 1 of each cycle:

Non-Hematologic Toxicity and/or dose discontinued within the previous cycle	
Toxicity/dose discontinued	Nab-Paclitaxel/Gemcitabine dose this cycle
Grade 0, 1 or 2 toxicity	Same as day 1 previous cycle
Grade 3 toxicity	Discontinue either one or both drugs until resolution to grade 0 or 1. Then resume treatment on the next lower dose level[a,b]
Grade 4 toxicity	Take off study[a]

Dose discontinued in 2 previous consecutive cycles	Discontinue either one or both drugs until resolution to grade 0 or 1. Then resume treatment on the next lower dose level[a,b]

a. This decision as to which drug should be modified will depend upon the type of non-hematologic toxicity seen and which course is medically most sound in the judgment of the investigator.

b. Pulmonary embolism (a grade 4 toxicity) if mild or asymptomatic will be exempt from this requirement. Grade 4 neuropathy will be exempt from this requirement (see section peripheral neuropathy for recommendations)

Dose modifications for non-hematologic toxicity within a cycle

CTC grade	**Percent of day 1 treatment dose**
0-2 (and grade 3 nausea/vomiting, alopecia)	100%
3 (except nausea/vomiting, alopecia)	Discontinue either one or both drugs until resolution to grade 0 or 1. Then resume treatment on the next lower dose level[a]
4	Hold[a, b]

a. This decision as to which drug should be modified will depend upon the type of non-hematologic toxicity seen and which course is medically most sound in the judgment of the investigator.

b. Pulmonary embolism (a grade 4 toxicity) if mild or asymptomatic will be exempt from this requirement. Grade 4 neuropathy will be exempt from this requirement (see section peripheral neuropathy for recommendations)

Peripheral Neuropathy: Dose modifications for day 1 and within each cycle

Peripheral neuropathy	
CTC grade	nab-Paclitaxel/Gemcitabine dose
Grade 0, 1 and 2	100 %
Grade 3 and 4	Nab-Paclitaxel should be discontinued until neuropathy improves to Grade 0 or 1, resume nab-Paclitaxel at next lower dose level[a,b]. Gemcitabine can be continued without dose modification.

a. Patients experiencing peripheral neuropathy that requires a delay in scheduled nab-Paclitaxel dosing for ≥ 21 days will be discontinued from further participation in this study.

b. The time to resolution to grade 0 or 1 should be the adverse event duration used for adverse event reporting.

Cutaneous toxicity: Dose modifications for day 1 and within each cycle

Cutaneous toxicity	
CTC grade	Nab-Paclitaxel/Gemcitabine dose
Grade 0, 1	100 %
Grade 2 or 3	Nab-Paclitaxel and Gemcitabine dose should be reduced to the next lower dose level, discontinue treatment if toxicity persists

Gastrointestinal toxicity: Dose modifications for day 1 and within each cycle

Gastrointestinal toxicity	
CTC grade	Nab-Paclitaxel/Gemcitabine dose
Grade 0, 1 and 2	100 %
Grade 3	nab-Paclitaxel and Gemcitabine should be discontinued until GI toxicity improves to Grade 0 or 1 resume at next lower dose level[a]

a. The time to resolution to grade 0 or 1 should be the adverse event duration used for adverse event reporting.

If feasible, the chemotherapy combination will be administered until intercurrent diagnosis of disease progression (according to RECIST 1.1 criteria). If not prevented by fulminating early progression or severe toxicity, a minimum two cycles should be applied. Maintenance treatment with Gemcitabine is allowed if nab-Paclitaxel has to be stopped due to toxicity. If nab-Paclitaxel has to be stopped due

to peripheral neuropathy grade 3 or 4, nab-Paclitaxel should be resume at the next lower level if neuropathy improves to grade 0 or 1.

Response was to be assessed on CT- or MRI-scans every 8 weeks until progression of disease. Patients that stopped all study treatment before having reached progression of disease remained in the study and were to be assessed for response every 8 weeks.
Patient questionnaires had to be filled in at baseline, every 4 weeks after start of therapy, at end of study treatment, and at each follow-up visit.

Within this clinical trial a concomitant project was performed. To determine predictive factors for tumor response and toxicity, biomarker analysis was planned in blood samples and tumor tissue.

6.2 Selection of Study Population / Study Subjects

All data related to patients were assessed pseudonymously. Each patient was clearly identified through the patient number given during the enrolment procedure. At the center site the Investigator compiled a confidential list, in which the patient name and address were assigned to the patient number.
The selection of patients occurred through the investigator according to the inclusion and exclusion criteria after having informed the patient in writing and orally about the study and after the patient had signed the informed consent. There was no preferred enrolment of men or women within this study. However, pregnant or breast-feeding women were excluded from participation.
Registration was possible 24 h a day.

6.2.1 Inclusion Criteria

Patients were included in the study only if they met all the following criteria:

- signed informed consent before start of specific protocoll procedure
- age > 18 years
- histologically or cytologically documented diagnosis of cholangiocellular carcinoma, bile duct cancer or gall bladder carcinoma
- presence of at least one measurable site of disease following RECIST 1.1 criteria
- unresecable, metastatic or recurrent disease
- ECOG performance 0 or 1
- life expectancy of at least 3 months
- any contraindication for Cisplatin, i.e. renal impairment (creatinine clearance < 60 ml/min), impaired hearing, increased risk or history for thromboembolic events, intolerance of extensive hydration, left ventricular ejection fraction (LVEF) < 45%)
- adequate bone marrow, liver and renal function as assessed by the following laboratory requirements to be conducted within 7 days prior to screening
  - absolute neutrophil count (ANC) ≥ 1500/mm³
  - platelet count ≥ 100.000/µl
  - total bilirubin < 3 x ULN and and sufficient biliary drainage
  - ALT and AST < 3 x ULN, < 5 x ULN if liver metastasis present
  - PT-INR/PTT < 1.5 x ULN, patients therapeutically anticoagulated with NMH, heparin or NOACs (dabigatran, rivaroxaban, abixaban) are allowed to participate, patients anticoagulated with phenoprocoumon or warfarin should be switched to NMH, heparin or NOACs
  - creatinine clearance ≥ 30 ml/min and serum creatinine ≤ 2.5 x ULN
- confirmed menopause, negative pregnancy test within 7 days of the start of treamtent and willingness to use highly effective methods of contraception
- willingness and able to comply with the protocol for the duration of the study

6.2.2 Exclusion Criteria

Patients were excluded from the study for any of the following reasons:

- no prior anti-cancer chemotherapy or radiotherapy for metastatic, advanced or recurrent disease; adjuvant/additive chemotherapy or radiotherapy after resection is allowed if therapy free intervall is at least 4 months; concomitant small volume palliative radiotherapy of bone metastases are allowed
- investigational drug therapy during or within 4 weeks of study entry
- major surgery within 4 weeks of starting therapy within this study
- symptomatic brain metastasis
- clincially significant cardiovascular disease (incl. Myocardial infarction, unstable angina, symptomatic congestive heart failure, serious uncontrolled cardiac arrhythmia) 6 months before enrollment
- active clinically serious infections (> grade 2 NCI-CTC version 4.0)
- history of interstitial lung disease
- liver cirrhosis child-pugh score > 8
- history of HIV infection or chronic hepatitis B or C
- pre-exisiting neuropathy > grade 1 (NCI-CTC version 4.0)
- patients with evidence of bleeding diathesis
- patients with second primary cancer within 5 years, exept adequately treated basal skin cancer or carcinoma in-situ of the cervix or bladder, or low/intermediate risk prostate cancer (Gleason score ≤ 7) with normal PSA levels
- any condition that could jeopardize the safety of the patient and their compliance of the study
- breast-feeding patients
- substance abuse, medical, psychological or social conditions that may interfere with the participation in the study

6.2.3 Removal of Patients from Therapy or Analysis

The following events were sufficient for withdrawal of a patient from study treatment, however, collection of follow-up data was possible:

- Severe adverse events according to NCI-CTCAE version 4.0
- Discontinuation of therapy for more than 21 days because of toxicities
- Decision of the investigator, if further treatment was not beneficial for the patient
- Progressive disease
- Non-Compliance of the patient

Patients had to be withdrawn from study treatment and procedures (including follow-up visits), for the following reasons:

- Withdrawal of the patient’s informed consent
- Patient was lost to follow-up
- Death

Withdrawn patients were not replaced.

6.3 Interventions

6.3.1 Investigational Medicinal Products

All enrolled received a therapy regimen of Gemcitabine and nab-Paclitaxel. The dose will be adjusted based on the bilirubin level.

Bilirbin ≤ 1.5x ULN

- Gemcitabine 1000 mg/m² i.v. day 1, 8, 15
- nab-Paclitaxel 125 mg/m² i.v. day 1, 8, 15

repeat the cycle at day 28, until disease progression

Bilirubin > 1.5 - 3 x ULN

- Gemcitabine 800 mg/m² i.v. day 1, 8, 15
- nab-Paclitaxel 100 mg/m² i.v. day 1, 8, 15

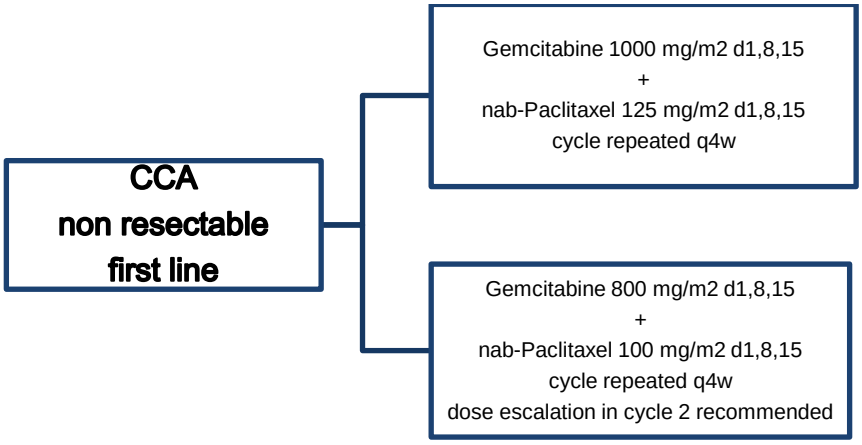
repeat the cycle at day 28, until disease progression

dose escalation in cycle 2, if cycle 1 was tolerated without significant toxicities (grade 3 or 4) to

- Gemcitabine 1000 mg/m² i.v. day 1, 8, 15
- nab-Paclitaxel 125 mg/m² i.v. day 1, 8, 15

repeat the cycle at day 28, until disease progression

Treatment was continued until progressive disease was documented or unacceptable toxicity occurred.



6.3.2 Description of Investigational Medicinal Products

Gemcitabine and nab-Paclitaxel are commonly used and registered for the palliative treatment of pancreatic cancer. However, this chemotherapy combination is not registered for treatment of biliary tract cancer. The investigational study drug in this trial is nab-Paclitaxel only. As Gemcitabine is generally available and form the routine treatment of advanced biliary tract cancer, it is considered as chemotherapy backbone medication. Thus, the latter drug was prescribed by the treating physician, as this prescription is within the framework of standard, recommended usage. The supply with nab-Paclitaxel was supported by Celgene GmbH as a research grant.

Gemcitabine:

Gemcitabine was administered according to the respective package inserts and local routine.

The most commonly reported side effects associated with Gemcitabine treatment include: nausea with or without vomiting, elevated liver transaminases (AST / ALT) and alkaline phosphatase have been reported in 60% of patients; proteinuria and hematuria in 50% of patients dyspnea in 10-40% of patients (highest incidence in lung cancer patients); were reported allergic skin rashes occur in approximately 25% of patients and are associated with itching in about 10% of the patients. The frequency and severity of the reactions are affected by the dose, the infusion rate and the intervals between doses. Dose limiting side effects are decreases in platelet, leucocyte and granulocyte counts.

Nab-Paclitaxel:

Nab-Paclitaxel was administered according to the respective package inserts and local routine. Recommended dose of nab-Paclitaxel in combination with Gemcitabine in systemic treatment of adenocarcinomas of the pancreas is 125 mg/m² administered as an intravenous infusion over 30 minutes on days 1, 8 and 15 of each 28-day cycle. The recommended dose of Gemcitabine is 1000 mg/m² combination partner as an intravenous infusion over 30 minutes immediately following the nab-Paclitaxel administration on days 1, 8 and 15 of each 28-day cycle.

6.3.3 Method of Assigning Subjects to Investigational Medicinal Products / Randomization

The Doses of gemcitabine and nab-Paclitaxel were assigned according to the bilirubin level of the patiens.

6.3.4 Dose Selection

Patients with bilirubin ≤ 1.5x ULN recieved chemotherapy with nab-Paclitaxel/Gemcitabine (nab-Paclitaxel 125 mg/m^2/30 min and Gemcitabine 1000 mg/m^2/30 min on day 1, 8 and 15 of a 28 day-cycle treatment period).
Patients with bilirubin > 1.5-3x ULN received chemotherapy with nab-Paclitaxel/Gemcitabine (nab-Paclitaxel 100 mg/m^2/30 min and Gemcitabine 800 mg/m^2/30 min on day 1, 8 and 15 of a 28 day-cycle treatment period) in the first cycle. If cycle 1 was tolerated without significant toxicities (grade 3 or 4), dose esclation (nab-Paclitaxel 125 mg/m^2/30 min and Gemcitabine 1000 mg/m^2/30 min on day 1, 8 and 15 of a 28 day-cycle treatment period) was recommended in cycle 2.

6.3.5 Selection and Timing of Dose for Each Patient

In case of adverse events dose reductions or delays were performed for each patient specifically.

6.3.6 Blinding

Not applicable.

6.3.7 Prior and Concomitant Therapy

Information about previous treatment for primary tumor was recorded in the source data and in the eCRF. All concomitant medication or medication administered within the 2 weeks preceding study start had to be recorded in the eCRF.
During treatment, all concomitant medications were recorded in the patient's source documentation as well as in the appropriate forms of the eCRFs. The generic or trade name, indication, start and stop dates had to be recorded.

Sedatives, antibiotics, analgesics, antihistamines, steroids, granulocyte-colony stimulating factor, erythropoetin, or other medications as well as red blood cells, platelets or fresh frozen plasma transfusions could be given to assist in the management of pain, infection, and other complications of the malignancy.
Patients could be pre-medicated before chemotherapy infusions according to local standard routine.

Additional concurrent chemotherapy or radiation therapy could not be administered during study therapy.

6.3.8 Compliance

Patients received treatment under the supervision of a physician experienced in the use of antineoplastic medicinal products.

6.4 Efficacy and Safety Variables

6.4.1 Efficacy and Safety Variable Measurements, and Flow Chart

The following baseline examinations were performed within **28 days** before start of treatment and included:

- Signed written informed consent.
- CT or MRI of the abdomen
- Additional tumor assessment by imaging techniques (e.g. CT/MRI/Xray of the thorax, bone scan), if clinically indicated
- CT of the brain, if clinically indicated
- Translational pathology performed at the institute of pathology of the university hospital Essen
- Complete medical history including dates and description of initial diagnosis of CCA, pre-treatment, relevant concurrent illnesses
- relevant concomitant medication.
- 12 lead ECG.
- Echocardiography.
- Spirometry and capillary blood gases.
- Physical examination including: weight, height, WHO/ECOG performance status, blood pressure, pulse rate and oral temperature, signs of ascites or encephalopathy.
- Current symptoms and/or residual toxicities from prior therapies should be recorded using the NCI Common Toxicity Criteria (CTCAE), Version 4.0.
- Relevant concomitant medication.
- Hematological tests: Complete blood count (CBC) including neutrophil and platelet count, sodium, potassium, chloride, calcium, magnesium, creatinine, blood urea nitrogen, GFR, uric acid, bilirubin (in case of elevated Bilirubin plus dir/indirect), AST, ALT, LDH, alk. phosphatase, total protein, albumin, TPZ, PT-INR, pTT, CRP
- Serological test for hepatitis B surface antigen (HBV sAg), hepatitis C antibody (HCV Ab) or hepatitis C RNA (HCV RNA), subjects who have tested positive for HCV Ab but negative for HCV RNA are allowed to enroll. HIV-1/-2 antibodies, including p24 antigene.
- Documentation of Child-Pugh score, including signs of ascites and encephalopathy.
- Tumormarker: CA19-9 and CEA
- Health related quality of life (HRQOL) assessment EORTC-QLQ-C30 and EORTC QLQ-BIL21
- Urine or serum HCG if patient is of childbearing potential.
- PAX-gene tube for translational research

- Translational blood probe for circulating free DNA (cfDNA), 7.5 ml EDTA-Plasma and 7.5 ml Serum
- Documentation of survival status.

The following baseline assessments/procedures were conducted or obtained within **seven days** prior to start of study treatment:

- Physical examination including: weight, height, WHO/ECOG performance status, blood pressure, pulse rate and oral temperature, signs of ascites or encelphalopathy.
- Current symptoms and/or residual toxicities from prior therapies should be recorded using the NCI Common Toxicity Criteria (CTCAE), Version 4.0.
- Relevant concomitant medication.
- Hematological tests: Complete blood count (CBC) including neutrophil and platelet count, sodium, potassium, chloride, calcium, magnesium, creatinine, blood urea nitrogen, GFR, uric acid, bilirubin, AST, ALT, LDH, alk. phosphatase, total protein, albumin, TPZ, PT-INR, pTT, CRP.
- Documentation of survival status.

During study treatment the following examinations were to be performed

Every Visit during treatment

- Hematological tests: Complete blood count (CBC) including neutrophil and platelet count, sodium, potassium, chloride calcium, magnesium, creatinine, blood urea nitrogen, GFR, uric acid, bilirubin, AST, ALT, LDH, alk. phosphatase, total protein, albumin, TPZ, PT-INR, pTT, CRP
- Physical examination including: weight, WHO/ECOG performance status, blood pressure, pulse rate, oral temperature and signs of ascites or encephalopathy.
- Relevant concomitant medication.
- Toxicity/adverse events (all that occurred during the previous cycle) according to the NCI Common Toxicity Criteria (CTCAE), Version 4.0.
- Documentation of survival status.

In addition, on day 1 of every second treatment cycle (Assessments during treatment could be counted for C1D1)

- Tumormarker: CA19-9 and CEA
- CT or MRI of the abdomen/pelvis
- Additional tumor assessment by imaging techniques (e.g. CT/MRI/Xray of the thorax, bone scan), if clinically indicated
- 12 lead ECG.
- Echocardiography.
- Spirometry and capillary blood gases.
- Translational blood probe for circulating free DNA (cfDNA), 7.5 ml EDTA-Plasma and 7.5 ml Serum
- Health related quality of life (HRQOL) assessment EORTC-QLQ-C30 and EORTC QLQ-BIL21
- Urine or serum HCG if patient is of childbearing potential. (only at C1D1)

At the end of treatment (EOT) (day 28 after start of last chemotherapy cycle)

- Physical examination including: weight, WHO/ECOG performance status, blood pressure, pulse rate, oral temperature, signs of ascites or encephalopathy
- Relevant concomitant medication.
- Toxicity/adverse events according to the NCI Common Toxicity Criteria (CTCAE), Version 4.0.

- Hematological tests: Complete blood count (CBC) including neutrophil and platelet count, sodium, potassium, chloride, calcium, magnesium, creatinine, blood urea nitrogen, GFR, uric acid, bilirubin, AST, ALT, LDH, alk. phosphatase, total protein, albumin, TPZ, PT-INR, pTT, CRP
- Tumormarker: CA19-9 and CEA
- Translational blood probe for circulating free DNA (cfDNA), 7.5 ml EDTA-Plasma and 7.5 ml Serum
- Health related quality of life (HRQOL) assessment EORTC-QLQ-C30 EORTC QLQ-BIL21
- Documentation of survival status.
- Urine or serum HCG if patient is of childbearing potential.

After the end of treatment (EOT) every 8 weeks

- Physical examination including: weight, WHO/ECOG performance status, blood pressure, pulse rate, oral temperature, signs of ascites or encephalopathy.
- Relevant concomitant medication.
- Toxicity/adverse events according to the NCI Common Toxicity Criteria (CTCAE), Version 4.0.
- Hematological tests: Complete blood count (CBC) including neutrophil and platelet count, sodium, potassium, chloride, calcium, magnesium, creatinine, blood urea nitrogen, GFR, uric acid, bilirubin, AST, ALT, LDH, alk. phosphatase, total protein, albumin, TPZ, PT-INR, pTT, CRP
- Tumormarker: CA19-9 and CEA
- CT or MRI of the abdomen/pelvis
- Additional tumor assessment by imaging techniques (e.g. CT/MRI/Xray of the thorax, bone scan), if clinically indicated
- Translational blood probe for circulating free DNA (cfDNA), 7.5 ml EDTA-Plasma and 7.5 ml Serum
- Health related quality of life (HRQOL) assessment EORTC-QLQ-C30 EORTC QLQ-BIL21
- Documentation of survival status.

At the end of the study (EOS/PD) (progressive disease or other reasons)

- Physical examination including: weight, WHO/ECOG performance status, blood pressure, pulse rate, oral temperature, signs of ascites or encelphalopathy.
- Relevant concomitant medication.
- Toxicity/adverse events according to the NCI Common Toxicity Criteria (CTCAE), Version 4.0
- Hematological tests: Complete blood count (CBC) including neutrophil and platelet count, sodium, potassium, chloride, calcium, magnesium, creatinine, blood urea nitrogen, GFR, uric acid, bilirubin, AST, ALT, LDH, alk. phosphatase, total protein, albumin, TPZ, PT-INR, pTT, CRP
- Tumormarker: CA19-9 and CEA
- CT or MRI of the abdomen/pelvis
- Additional tumor assessment by imaging techniques (e.g. CT/MRI/Xray of the thorax, bone scan), if clinically indicated
- 12 lead ECG.
- Echocardiography.
- Spirometry and capillary blood gases.
- Translational blood probe for circulating free DNA (cfDNA), 7.5 ml EDTA-Plasma and 7.5 ml Serum
- Health related quality of life (HRQOL) assessment EORTC-QLQ-C30 EORTC QLQ-

BIL21
- Documentation of survival status.

Follow-up documentation every 3 months for up to two years were mainly performed in order to assess the efficacy objectives of progression-free and overall survival. Staging procedures were only to be documented until unequivocal detection of progression.

- (Protracted) toxicity/adverse events findings according the NCI Common Toxicity Criteria (CTCAE), Version 4.0.
- CT or MRI of the abdomen
- Additional tumor assessment by imaging techniques (e.g. CT/MRI/Xray of the thorax, bone scan), if clinically indicated.
- Documentation of survival status.
- Second / further line treatment

For patients still alive at the termination of the 2-year follow-up period, additional information on OS and PFS was obtained by a fax survey at the time point of study closure.

An overview of the study procedures and observations is given in Table 1.

Table 1: Schedule of visits and assessments

Assessment	Screening	Pre-treatment	Treatment									EOT	Every 8 weeks after EOT	EOS/PD	Follow-up every 3 months
	Day-28 to -1	Day -7 to 0	C1 D1	C1 D8	C1 D15	C2 D1	C2 D8	C2 D15	C 3-X D1	C3-X D8	C3-X D15				
Signed Informed Consent	X														
Medical history	X														
Histology[1]	X														
Tumorsample (FFPE)	X														
pregnancy test	X		X									X		X	
Serological test for HIV, HCV, HBV	X														
Child-Pugh score, including documentation of ascites, encephalopathy)	X														
Tumor assessment[2]	X*								X*				X	X	X
ECG	X*								X*					X	
Echocardiography	X*								X*					X	
Spirometry and capillary blood gases	X*								X*					X	
Physical examination[3]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Concomitant medication	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Safety Laboratory[4]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Adverse events/Toxicity	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Ca19-9, CEA	X		X						X*			X	X	X	
Blood for translational research	X		X						X*			X	X	X	
Quality of life[5]	X		X			X			X			X	X	X	
Chemotherapy			X	X	X	X	X	X	X	X	X				

Survival status	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Second /further line treatment															x

[1]Histological or cytological proofed adenocarcinoma of the bililary tract

[2] Abdominal/Thorax CT or MRI for screening and during treatment every 8 weeks and at end of study if reason other than progressive disease

[3] This includes height (only at screening), weight, blood pressure, heart rate, and ECOG performance status., ascites

[4] Hemoglobin, hematocrit, platelet count, white blood count including differential blood count, sodium, potassium, chloride calcium, magnesium, creatinine, blood urea nitrogen, GFR, uric acid, bilirubin, AST, ALT, LDH, alk. phosphatase, total protein, albumin, TPZ, PT-INR, pTT, CRP

[5] Quality of life assessment should be performed even when the chemotherapy cannot be applied at the beginning of a cycle e.g. due to toxicity reasons

*every eight weeks during treatment

6.4.2 Appropriateness of Outcome Measures

Only standard efficacy or safety measures were uses. No surrogate markers were used as endpoints.

6.4.3 Primary Variable(s)

The primary endpoint of this study was the overall response rate [= patients with either complete response (CR) or partial response (PR) divided by the number of patients eligible for the ITT], using RECIST 1.1 criteria.
Each set of tumor responses was assessed to determine the best overall response according to RECIST criteria.

6.4.4 Determination of Study Drug Serum Concentrations

Not applicable.

6.5 Data Quality Assurance

The study site was responsible for the data documentation and for the maintenance of patient files. Essential documents were archived safely and securely, and were available upon authorities' request. All outcome variables and covariates were recorded in a standardized CRF. The Investigator had to ensure that all data entered into the CRF had available source documentation at the study site.

By signing the signature page of the study protocol the Investigator confirmed that he had read the protocol, understood it, and worked according to the protocol and to the ethical principles stated in version of 1996 of the Declaration of Helsinki, the applicable guidelines for good clinical practices, or the applicable laws and regulations of the country of the study site for which they were responsible, whichever provided the greater protection of the individual.

To initiate a site for the study, a site initiation visit was performed during which the investigator and the study staff were informed about the conduct of the clinical trial and the study documentation.

6.6 Statistical Methods Planned in the Protocol and Determination of Sample Size

6.6.1 Statistical Analysis Plan

All analyses predefined in the study protocol were planned in detail in the statistical analysis plan (SAP) which was created by Prof. Dr. Stefan Kasper-Virchow. The analyses conducted for the translational project were not part of the SAP.

The statistical evaluation was performed by Prof. Dr. Kasper, University Hospital of Duisburg-Essen using the software SSPS version 22.

The following analysis sets were scheduled:

Safety population (SP) = Intent-to-treat (ITT): All patients who received at least one dose of any study treatment (gemcitabine or nab-paclitaxel).

Per-protocol (PP) population: The PP is defined as the subset of the ITT analysis set who have received at least two cycles of combination therapy during the protocol treatment period (unless they experience unequivocally documented earlier progression according to RECIST 1.1) and who have no major protocol deviations thought to impact on the efficacy conclusions of the trial.

However, the last criterion could introduce a bias in favour of the new therapy and it was decided not to consider this criterion for the modified per protocol (mPP) set. It was also decided, that the data of the mPP set are only analysed for the CSR, if the difference in the number of patients between the PP and ITT sets is more than 5%, because in this case possible differences between the two sets are negligible and irrelevant for the conclusions of the study.

All efficacy variables (primary and secondary endpoints) were analyzed in the ITT set. The SP was used for the analyses of the safety variables.

All analyses, except the analysis of the primary endpoint, were exploratory.

The primary endpoint was the quantification of the responder-fraction (CR/PR) of patients with CCA ineligible for cisplatin treated with gemcitabine and nab-paclitaxel.

For each patient the objective response was determined. Complete and partial remissions were considered as showing a response.

Statistical analysis of experimental data occurred at the end of the study, after data base lock was performed. Variables of interest were determined for each study participant. Best overall response was assigned according to RECIST 1.1 criteria. Time to event endpoints were assigned the date of documented event occurrence. In the absence of such documentation, these endpoints were censored on the last known event-free date.

The analysis of primary efficacy relied on determination of exact 95% confidence limits for the binomial distribution. Published tables provide these statistics for specified sample size (e.g., Documenta Geigy).

The exploratory analysis of secondary variables relied on traditional methods. Time to event endpoints (e.g., duration of response, time to response, PFS, OS) were summarized by Kaplan-Meier estimates and presented in life-table format and graphically. If the data allowed, median time to event with a two-sided 95% confidence interval were determined. Continuous variables were summarized descriptively with the following statistics: mean, median, standard error of the mean, minimum and maximum. Additional binomial outcomes (e.g., disease control) employed the exact methods for the binomial distribution. Identical analytical methodology was applied to the ITT, Per-Protocol and any sub-populations of interest, however, the ITT results were deemed primary.

6.6.2 Sample Size

This is an explorative pilot trial with a cohort of 10 patients. So far no data for the efficacy of the combination of Gemcitabine and nab-Paclitaxel in CCA was available. In addition this study was conducted in a patient population with comorbidities and not eligible for the standard chemotherapy for this disease. This population is usually underrepresented in clinical trials. The major reason for conducting this pilot trial was to determine initial data in order to perform a sample size calculation for an expansion phase (single arm, or a randomized phase II trial) (Lancaster GA *et al.*, 2004). Usually 10 participants or 10% of the final study size are included in an explorative pilot trial (Nieswiadomy, 2002; Lackey and Wingate, 1998; Hully et al., 2001).

6.7 Changes in the Conduct of the Study or Planned Analytical Methods

During the course of the clinical trial there were no amendments, which included changes to the study conduct.

7 Study Population

7.1 Disposition of Study Patients

Altogether 10 patients were registered by 1 sites. Nine patients had bilirubin levels ≤ 1.5x ULN and started therapy with gemcitabine 1000 mg/m² i.v. day 1, 8, 15 and nab-paclitaxel 125 mg/m² i.v. day 1, 8, 15 and one patient had a bilirubin level > 1.5 - 3 x ULN and started therapy with gemcitabine 800 mg/m² i.v. day 1, 8, 15 and nab-paclitaxel 100 mg/m² i.v. day 1, 8, 15. All 10 patients had at least 1 study treatment cycle administered (SP and ITT); nine patients stopped therapy due to progression and one patient stopped due to a secondary resection. At the time of data cut-off (07/2020) all patients were dead.

Figure 1 gives an overview of patient disposition.

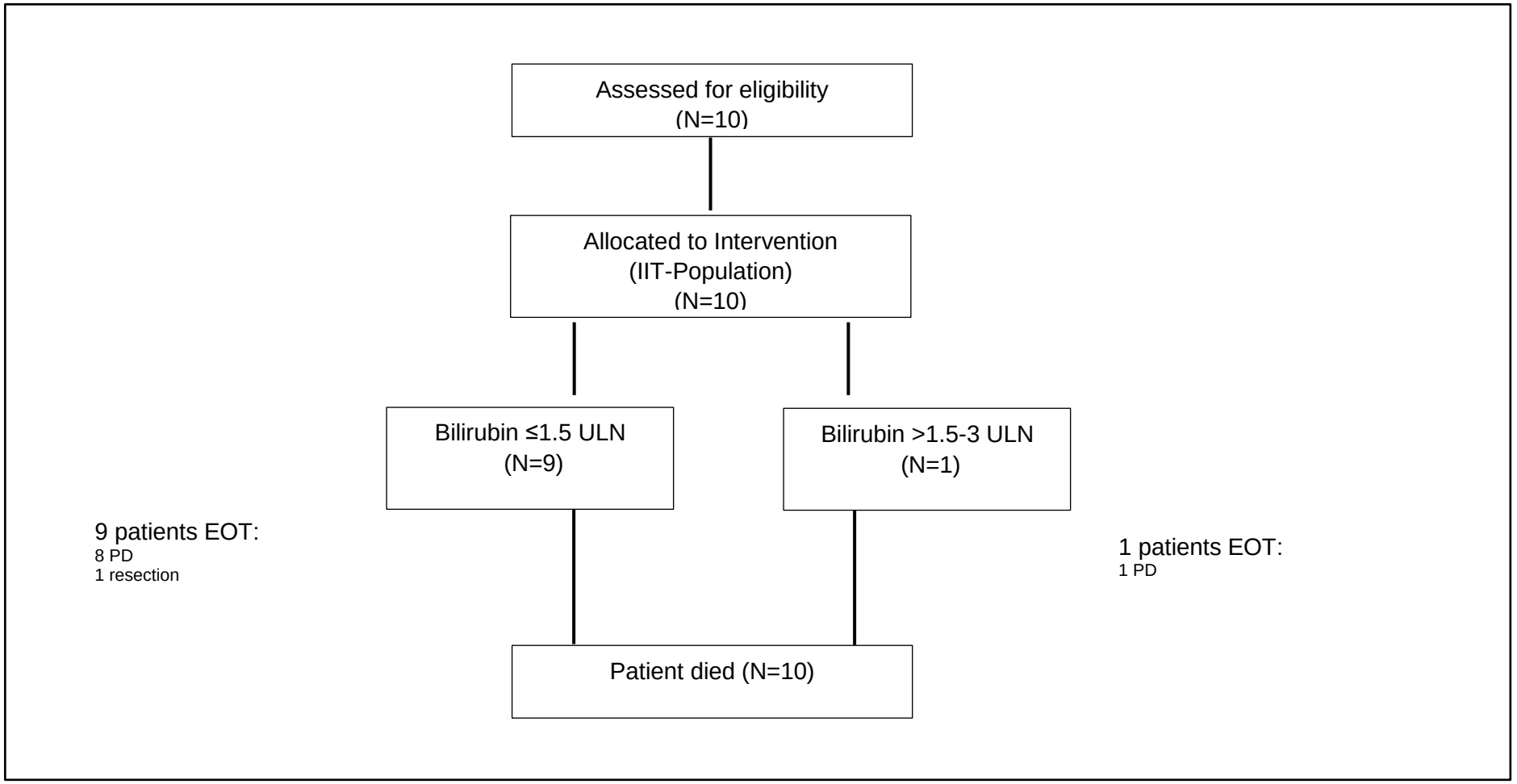


Figure 1: Disposition of patients

7.2 Recruitment

One site in Germany participated in the clinical trial and enrolled patients.
Recruitment period lasted from 06-Dec-2016 (first patient in) until 05-Jul-2017 (last patient in). In total 10 patients were registered and enrolled and were included into the ITT population.

After end of study therapy 10 patients began the follow-up. At time of data cut-off all 10 patients were dead
End of clinical trial (last patient last visit) was on 13-May-2020.

8 Efficacy Evaluation

8.1 Data Sets Analyzed

ITT set: All patients who received at least one dose of any study treatment (Gemcitabine or nab-Paclitaxel). 10 patients were included in ITT analysis set.

mPP set: The mPP set and the ITT set were identical, because the patients did not have any major protocol violations, and thus the presentation of mPP data in addition to the ITT data was useless.

Safety set: In the SAP this set was defined to be equal to the ITT set.

8.2 Demographic and Other Baseline Characteristics

Regarding patient characteristics at baseline there were no t differences between the 3 analysis sets because all sets were identical. In total set there were 60% women. Median (range) age amounted to 68 (59-70) years for ITT. Most of the patients started with an ECOG of 0.
A summary of patient characteristics is given in Table 2.

Table 2: Patient characteristics at registration

Parameter		ITT set (N=10)
Gender- N (%)	male	4 (40)
	female	6 (60)
Age [years]	median (range)	68 (59 - 70)
	mean (Std. Dev)	65 (6.2)
ECOG - N (%)	0	8 (80)
	1	2 (20)
Weight [kg]	median (range)	66.5 (59 – 80.9)
	mean (Std. Dev)	71.7 (18.1)
Height [cm]	median (range)	166 (162.5 - 174.0)
	mean (Std. Dev)	167.8 (8.0)
BMI [kg/m²]	median (range)	24.5 (21.1- 28.1)
	mean (Std. Dev)	25.0 (4.5)
Comorbidities - N (%)	yes	10 (100)
	no	0 (0)

All patients suffered from comorbidities; median number (range) of comorbidities per affected patient was 2 (1-4). Comorbidities were reported according to ICD-10. Most of the comorbidities occurred in single patients only. ‘Essential (primary) hypertension’ was the mainly reported disease (Table 3).

Table 3: Comorbidities at registration

Type of comorbidities (ICD10)	N (ITT set, N=10)
Essential (primary) hypertension	6
Presbycusis	3
Chronic ischaemic heart disease	2
Non-ST segment elevation myocardial infarction	1
Personal history of allergy to drugs, medicaments and biological substances	1
Chronic obstructive pulmonary disease, unspecified	1
Gastritis	1
Liver fibrosis	1
Hypothyreosis	1
Gastroesophageal cancer	1
Portal vein thrombosis	1
Gastric perforation	1
Pure hypercholesterolaemia	1
Recurrent Urinary tract infection	1
Liver cirrhosis	1
Non insulin dependant diabetes mellitus	1
Atherosclerosis of arteries of extremities	1
Pulmonary embolism	1
Stenosis of carotid artery	1

Reasons for Ciplatin ineligibility are listed in table 4. Main reasons were known presbycusis (N=3), coronary heart disease with insufficiency/cardiovascular disease (N=3) and thromboembolic events (N=2).

Table 4: Reason for Ciplatin ineligibity

Reason	N (ITT set, N=10)
Presbycusis	3
Chronic ischaemic heart disease with insufficieny/cardiovascular disease	3
Thromboembolic events	2
Chronic obstructive pulmonary disease	1
Ascites with contraindication for extensive hydrating	1

Data regarding primary tumor at baseline are shown in Table 5. The majority of patients had perhilar CCA (N=6) or intrahepatic CCA (N=2). Histology of primary tumors was adenocarcinoma. Grading was mainly G2.

Table 5: Characteristics of primary tumor at baseline

Tumor characteristics	ITT set (N=10)	
	N	%
Perihilar CCA	6	60
Intrahepatic CCA	2	20
Distal extrahepatic CCA	1	10
Gallbladder cancer	1	10
Histology		
adenocarcinoma	10	100
Grading		
G1	0	0
G2	7	70
G3	2	20
G4	0	0
Gx	1	10
T-stage (initial)		
T0	2	20
T1	1	10
T2	1	10
T3	3	30
T4	1	10
Tx	2	20
N-stage (initial)		
N0	5	50

Tumor characteristics	ITT set (N=10)	
	N	%
N1	5	50
Nx	0	0
M-stage (initial)		
M0	1	10
M1	9	90
Mx	0	0

Half of the patients (50%) were primary resected and had a relapse at time of registratrion; the other 50% of patients had non-resectable disease or synchronous metastases (Table 7).

Table 6: Primary therapy and status at registration

Primary therapy	ITT set (N=10)	
	N	%
resection	5	50
Adjuvant chemotherapy	1	10
Primary biliary tract stenting	3	30

Status at registration		
Non-resectable	2	20
Synchronous metastases	3	30
Relapse/metchronous metastases	5	50

Most patients (90%) had metastatic disease at the time of registration which were mostly localized at liver (Table 7).

Table 7: Localization of metastases at baseline

Localization of distant metastases	ITT set (N=10)
	N
Liver	3
Lung	3
Lymph nodes	3
Peritoneal carcinomatosis	3

Time between primary diagnosis and enrollment in the study amounted to a median (range) of 1.74 (0.43-40.21) months between diagnosis and enrolment into the study. (Table 8).

Table 8: Time from diagnosis

Time period [months]		ITT set (N=57)
Time from primary diagnosis to enrollment	median (range)	1.74 months (0.45 – 40.21)
	mean (Std.Dev.)	10.28 months (14.4)

8.3 Duration of study therapy

Study treatment was to be given until progression or unacceptable toxicities or patient's wish. Results are shown in Table 9. Patients received a mean of 6.6 and a median of 6 cycles, respectively.

Table 9: Treatment duration

Treatment duration		ITT set (N=10)
Months	mean (Std. Dev)	5.47 (1.83)
	median (range)	5.24 (3.22 – 9.43)
Cycles	mean (Std. Dev)	6.6 (2.32)
	median (range)	6 (4 -12)

The documented reason for terminating study treatment was mainly 'progressive disease' (90%) followed by secondary resection (10%) (Figure 2).

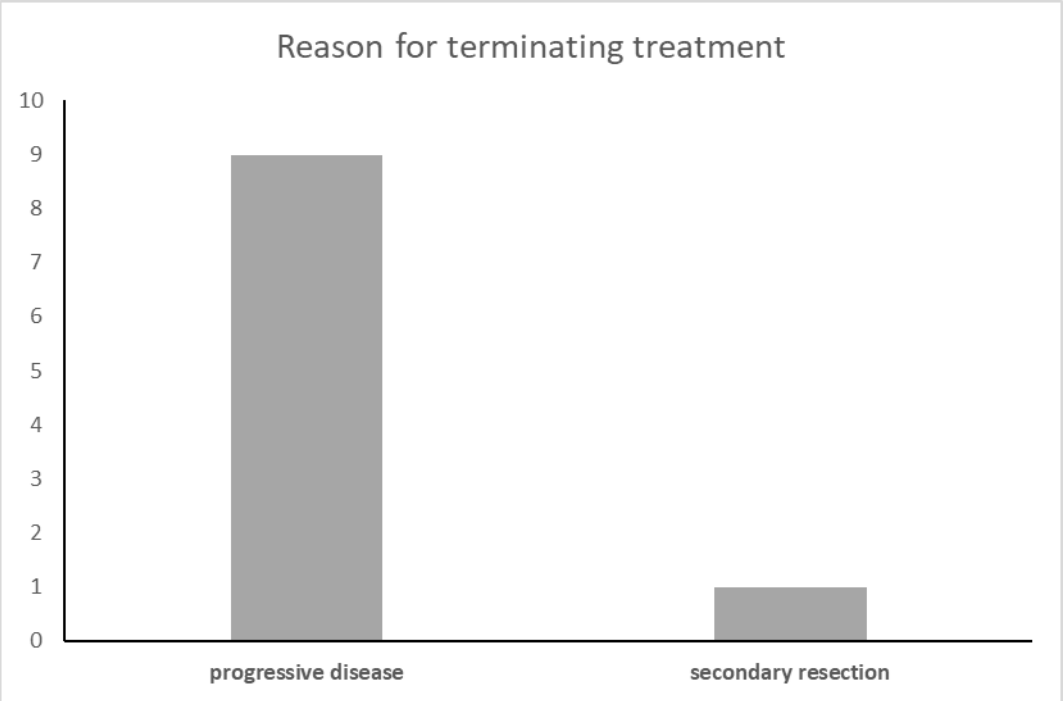


Figure 2: Reason for termination

8.4 Follow up period

The follow up period was assessed from date of registration to death, last patient contact for patients, who were lost to follow up or to date of data lock for all alive patients (01.07.2020). At time of data lock, all patients were dead.
Median follow-up period was 7.8 months for patients of ITT (Table 10).

Table 10: Follow up period [months]

N=10	Censored/death N (%)	Mean (Std. Dev)	Median (range)
	10 (100%)	11.9 (2.9)	7.8 (5.89 – 36.27)

8.5 Efficacy Analysis Results

8.5.1 Efficacy Analysis: Primary objective

Primary objective was the overall response rate (ORR) according to RECIST 1.1 criteria. ORR was defined by the proportion of patients with CR+PR as best response. Table 11 presents best responses as well as ORR in the ITT population. The ORR was 40%.

Table 11: Objective response rate

Objective response	ITT set (N=10) N	%	95% CI
Complete remission (CR)	0	0	0.0
Partial response (PR)	4	40.0	10.0;70.0
Stable disease (SD)	4	40.0	10.0;70.0
Progressive disease (PD)	2	20.0	0.0;50.0
ORR (CR+PR)	4	40.0	10.0;70.0

8.5.2 Efficacy Analysis: secondary objectives

Secondary objectives were

- Disease control rate (DCR) (complete remission, partial remission and stable disease)
- Progression free survival (PFS)
- PFS rate at 6 months
- Overall survival (OS)
- Serological response (decrease in CA19-9 levels)
- Toxicity/safety (reported in section 9)

8.5.2.1 Disease control rate (DCR)

Secondary objective was the disease control rate (DCR) according to RECIST 1.1 criteria. DCR was defined by the proportion of patients with CR+PR+SD as best response. Table 112 presents disease control rate (DCR) in the ITT population. The DCR was 80%, 20% had a progressive disease at the first evaluation.

Table 12: Objective response rate

Objective response	ITT set (N=10)		
	N	%	95% CI
Complete remission (CR)	0	0	0.0
Partial response (PR)	4	40.0	10.0;70.0
Stable disease (SD)	4	40.0	10.0;70.0
Progressive disease (PD)	2	20.0	0.0;50.0
DCR (CR+PR+SD)	8	80.0	50.0;100.0

8.5.2.2 Progression free survival (PFS)

Results of analysis of PFS are shown in Table 13a, b. All patients had progressive disease at time of data cut-off.

Patients had a median PFS of 5.7 months and a mean PFS of 7.2 months. 100% of patients had documented PD or death within study period.

Table 13a:

N=10	Median (months)	95% CI		Min	Max	Event (PD or death)	
						events	%
	5.717	5.309	6.124	4.172	15.704	100	100

Table 14b:

N=10	Mean (months)	95% CI		Std. Dev.	Event (PD or death)	
					events	%
	7.172	5.072	9.272	1.071	100	100

The following Figure 5 displays the Kaplan-Meier plots of PFS analysis.

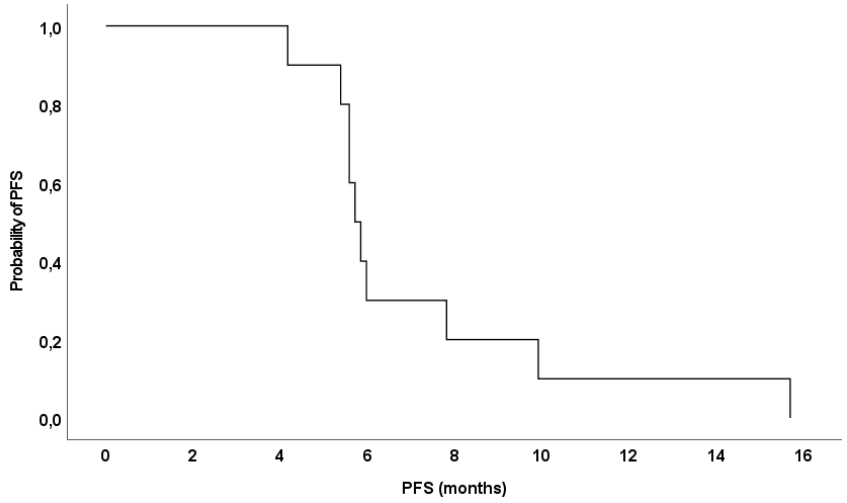


Figure 5: Kaplan Meier plots of PFS

8.5.2.1 Progression free survival (PFS) at 6 months

PFS Rate at 6 monhts is shown in Table 135. Thre patients had no progressive disease at 6 months.

Table 15: PFS rate at 6 months

PFS at 6 months	ITT set (N=10)		
	N	%	95% CI
Yes	3	30.0	0.0; 60.0
no	7	70.0	40.0;100.0

8.5.2.2 Overall survival (OS)

Results of analysis of OS are presented in Table 16a, b. At time of data cut-of, all patients were dead.

Median OS amounted to 7.8 months for ITT patients. Mean OS was 11.9 months. 100% of patients had documented death within study period.

Table 16a: median Overall survival

N=10	Median (months)	95% CI		Min	Max	Events (Death)	
						events	%
	7.819	5.444	10.195	5.881	36.271	10	100

Table 17b: mean Overall survival

N=10	Mean (months)	95% CI		Std. Dev.	Events (Death)	
					events	%
	11.900	6.189	17.611	2.914	10	100

Fehler! Verweisquelle konnte nicht gefunden werden. shows the Kaplan-Meier plots of OS analysis.

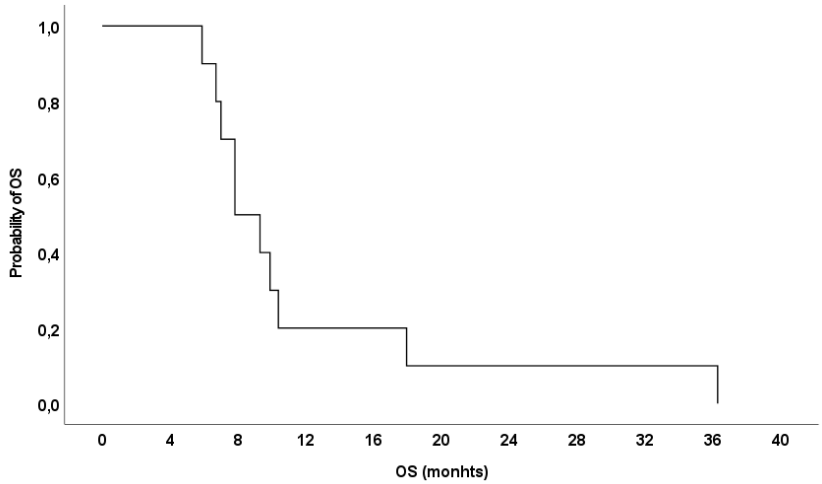


Figure 6: Kaplan Meier plots of OS

8.5.2.3 Serological response

In total seven out of 10 patients had elevated CA19-9 levels at time of registration. All of these seven patients had a decrease in CA19-9 after start of therapy.

Table 17: CA19-9 decrease

N=7	Median (%)	95% CI		Min	Max	Mean (%)	95% CI		Std. Dev.
	-83.05	-90.50	-52.41	-97.99	-43.11	-76.56	-90.25	-61.74	20.65

Fehler! Verweisquelle konnte nicht gefunden werden.7 shows the Waterfall-blot of CA19-9 decrease with the respective patient number

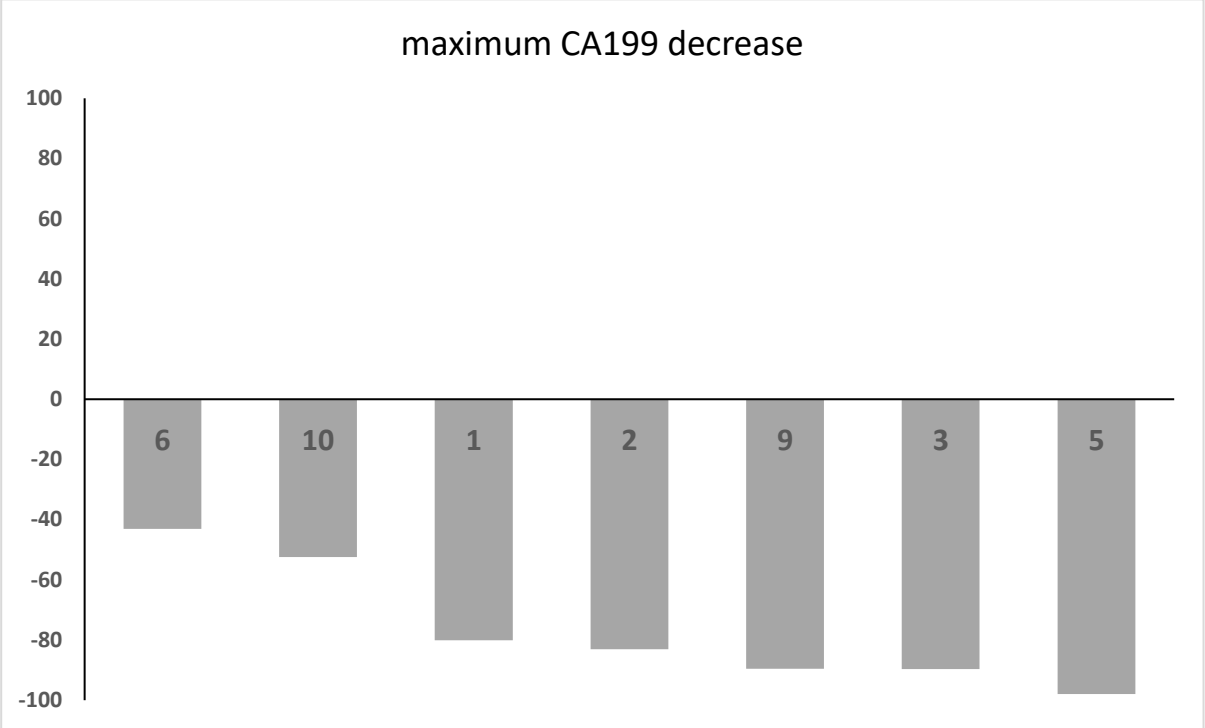


Figure 7: Waterfall-blot of CA19-9 decrease

8.5.3 Efficacy Analysis Conclusion(s)

Primary objective was the ORR (CR+PR) according to RECIST 1.1 criteria. The ORR was 40% with no CR and 4 PR out of 10 patients. The DCR (CR+PR+SD) was 80% with 8 patients with at least stable disease at first evalautation after 2 months therapy. All patients with elevated CA19-9 levels at registration had a decrease during therapy with a mean maximum decrease of 76.6%. Median and mean PFS were 5.7 and 7.2 months with 3 patients (30%) being without progressive disease at 6 months. Median and mean OS were 7.8 and 11.9 months, respectively in the ITT set.

9 Safety Analysis

9.1 Extent of Exposure

Patients in the safety set received a median of 6 cycles each (Table 9). Median duration iof therapy was 5.24 months (95% CI: 3.22-9.43).

Study therapy was to be administered on Day 1, 8 and 15, every 4 week. Therapy delays were documented in 15 cases for chemotherapy; 14 times for boths drugs and 1 time only for gemcitabine. Dose reductions were documented in 8 cases; 6 times for boths drugs, 1 time for nab-paclitaxel only and 1 time for gemcitabine. Main reason for delay or dose reduction were toxicity. Permanent discontinuation of one or nboth study drugs were documented in 6 cases; 2 times for both drugs and 4 times only for nab-Paclitaxel. Main Reason for permanent discontinuation was toxicity.

Table 18: Treatment delay

Treatment delay	Safety set	
	Number of delays	% of all delays
Gemcitabine delays (number)	15	100.0
Reason for delay		
- Toxicity	14	93.3
- Patient wish/logistic reasons	1	6.7
Nab-Paclitaxel delays (number)	14	100.0
Reason for delay		
- Toxicity	13	92.9
- Patient wish/logistic reasons	1	7.1

In total 6 out of 10 patients had treatment delays. (Table 19).

Table 19: Number of patients with therapy delay

Analysis set	Gemcitabine – Number of patients with delay		Nab-Paclitaxel– Number of patients with delay	
	N	%	N	%
Safety set (N=10)	6	60.0	6	60.0

Study treatment was 1000mg/m² Gemcitabine and 125mg/m² nab-Paclitaxel for patients with bilirubin levels ≤1.5xULN and 800mg/m² Gemcitabine and 100mg/m² nab-Paclitaxel for patients with bilirubin levels >1.5-3xULN. Nine patients had bilirubin levels ≤1.5xULN and stared with the full dose of both cytotoxic drugs, one patient had a bilirubin level >1.5xULN and started with die reduced doses. Dose reductions were evaluated for each drug separately (Table 20).

Table 20: Total number of dose reductions

Drug	Safety set Number of dose reductions
Gemcitabine	6
Nab-Paclitaxel	6

In total 6 out of 10 patients had dose reductions. (Table 1921).

Table 21: Number of patients with dose reduction(s)

Drug	Safety set (N=10)	
	N	%
Gemcitabine	5	50.0
Nab-Paclitaxel	6	60.0

Cumulative dose of Gemcitabine and nab-Paclitaxel is presented in Table 22.

Table 22: Cumulative dose received [mg]

Drug		Safety set (N=10)
Gemcitabine	median (range)	13896.5 (12057 - 16147)
	mean (Std. Dev.)	14072 (2395.9)
Nab-Paclitaxel	median (range)	1618 (1248 - 1818)
	mean (Std. Dev.)	1576.3 (329.3)

9.2 Adverse Events

Safety was one of the secondary objectives. Analysis of safety parameters was performed on patients of safety set. Adverse events (AEs) and serious adverse events (SAEs) reported by the sites were coded according to MedDRA.

9.2.1 Brief Summary of Adverse Events

Altogether 153 AEs, related and non-related, were reported in 10 patients. The great majority of AEs (120 AEs) were of NCI grade 1 or 2; 20 AEs were of NCI grade 3 or 4 and 13 were nor assessed for grade. There was no AE grade 5 documented. 84 AEs were reported as related to study medication. Most of AEs belonged to System Organ Class (SOC) ‘Blood and lymphatic system disorders’, ‘skin and subcutaneous tissue disorders’, ‘gastrointestinal disorders’ and ‘General disorders and administration site conditions’. Most frequent reported preferred terms (PT) were ‘Peripheral sensory neuropathy’, ‘Asthenic conditions’, ‘Diarrhoea’ and ‘Thrombocytopenia’ in 5, 6, 6 and 6 patients, respectively.

9.2.2 Presentation of Adverse Events

Table 27 in section 11.2 lists all reported AEs.

9.2.3 Treatment related AEs (TRAEs)

Most common TRAEs of grade ≥ 3 are shown in Table 23 and 24. Of these 14 TRAEs, the great majority were hematological AEs (Anaemia, Neutropenia, Thrombocytopenia) followed by non-hematological AEs affecting the nervous system.

Table 23: Most common treatment related AEs (TRAEs) of grade ≥ 3, number of AEs

SOC Term	Preferred Term	NCI grade 3		NCI grade 4		Total number of TRAE
		Related	n.e.	Related	n.e.	R+n.e.
Blood and lymphatic system disorders	Anaemia	3				3
Blood and lymphatic system disorders	Neutropenia	2		1		3
Blood and lymphatic system disorders	Leukopenia			1		1
Blood and lymphatic system disorders	Thrombocytopenia	2				2
Nervous system disorders	Peripheral sensory neuropathy	2				2
General disorders and administration site conditions	Pyrexia	2				2
Gastrointestinal disorders	Diarrhoea		1			1

n.e.: not evaluated

Table 24: Number of patients with treatment related AEs (TRAEs) of grade ≥ 3, number and frequency

SOC Term	PT Term	Number of patients with TRAE grade ≥3		% (N=10)
		Related	n.e.	
Blood and lymphatic system disorders	Anaemia	3		30%
Blood and lymphatic system disorders	Neutropenia	2		20%
Blood and lymphatic system disorders	Leukopenia	1		10%
Blood and lymphatic system disorders	Thrombocytopenia	2		20%
Nervous system disorders	Peripheral sensory neuropathy	1		10%
General disorders and administration site conditions	Pyrexia	2		20%
Gastrointestinal disorders	Diarrhoea		1	10.0%

n.e.: not evaluated

9.2.4 Deaths, Serious Adverse Events, and Significant Adverse Events

In total, 13 AEs were assessed as serious in 6 patients (60% of the safety set) by the investigator, 6 of these were related to study medication (marked green). Reason for seriousness was in all cases ‘hospitalisation’. Most of SAEs belonged to System Organ Class (SOC) ‘gastrointestinal disorders’ or ‚infections and infestations’. All SAEs recovered. No suspected unexpected serious adverse reactions (SUSARs) occurred.

Table 25: Listing of SAEs

SAE-ID	Patient ID	System Organ Class (Term)	System Event PT Term	Event	NCI grade	Start Date	Outcome	Reason for SAE	Gemcitabine-Relation	Nab-Paclitaxel - Relation
1	001-01	Gastrointestinal disorders	Diarrhoea	Diarrhea	3	24.12.2016	resolved	In-patient hospiatlization or prolongation	possible	possible
2	001-05	Hepatobiliary disorders	Bile duct infections and inflammations	Cholangitis	3	13.04.2017	resolved	In-patient hospiatlization or prolongation	Not related	Not related
3	001-02	Gastrointestinal disorders	Stomatitis	Stomatitis	2	20.05.2017	resolved	In-patient hospiatlization or prolongation	Not related	possible
4	001-07	Infections and infestations	Infection	Infection	3	18.10.2017	resolved	In-patient hospiatlization or prolongation	Not related	Not related
5	001-07	Infections and infestations	Respiratory tract infection	Respiratory infection	3	05.10.2017	resolved	In-patient hospiatlization or prolongation	Not related	Not related
6	001-05	General disorders and administration site conditions	Pain	Pain	3	19.09.2017	resolved	In-patient hospiatlization or prolongation	Not related	Not related
7	001-01	General disorders and administration site conditions	Pyrexia	Fever	3	06.02.2017	resolved	In-patient hospiatlization or prolongation	possible	possible
8	001-02	Gastrointestinal disorders	Stomatitis	Stomatitis	2	18.04.2017	resolved	In-patient hospiatlization or prolongation	possible	possible
9	001-04	Infections and infestations	Respiratory tract infection	Respiratory infection	2	07.08.2017	resolved	In-patient hospiatlization or prolongation	possible	possible
10	001-04	Infections and infestations	Respiratory tract infection	Respiratory infection	2	20.07.2017	resolved	In-patient hospiatlization or prolongation	possible	possible
11	001-07	Vascular disorders	Subclavian vein thrombosis	Subclavian vein thrombosis	3	14.06.2017	resolved	In-patient hospiatlization or prolongation	Not related	Not related
12	001-09	Gastrointestinal disorders	Constipation	Obstipation	2	16.02.2018	resolved	In-patient hospiatlization or prolongation	Not related	Not related
13	001-09	Gastrointestinal disorders	Vomiting	Emesis	3	26.02.2018	resolved	In-patient hospiatlization or prolongation	Not related	Not related

For all 10 patients of safety set, death was reported at the end of study documentation.

Table 26: Patients died

Analysis set	Patients who died	
	N	%
Safety set (N=10)	10	10.0

9.3 Analysis and Discussion of Deaths, SAEs, and Significant AEs

In total 153 AEs were reported in 10 patients (= ITT/safety set); of these 84 AEs were related to study medication in 10 patients (100% of the safety set). 20 AEs were of grade 3-4. No grade 5 AE was reported. Outcome of AEs was mainly ‘recovered’. The great majority of TRAEs of grade 3-4 were hematological AEs (Anaemia, Neutropenia and Thrombocytopenia) followed by non-hematological AEs affecting the nervous system.

Most of AEs belonged to System Organ Class (SOC) ‘Blood and lymphatic system disorders’, ‘skin and subcutaneous tissue disorders’, ‘gastrointestinal disorders’ and ‘General disorders and administration site conditions’. Most frequent reported preferred terms (PT) were ‘Peripheral sensory neuropathy’, ‘Asthenic conditions’, ‘Diarrhoea’ and ‘Thrombocytopenia’ in 5, 6, 6 and 6 patients, respectively.

13 AEs were assessed as serious in 6 patients (60% of the safety set) by the investigator, of which 6 were related to study medication. Six and 4 SAEs belonged to SOC and ‘gastrointestinal disorders’ and ‘infections and infestation`, respectively. All SAEs recovered.

9.4 Safety Analysis Conclusion(s)

The combination gemcitabine and nab-paclitaxel was well tolerated in these patient population with CCA ineligible for Cisplatin based chemotherapy. The reported AEs/SAEs were in accordance with the SmPC of the respective study drugs.
Most of the reported AEs were of grade 1 or 2. Nearly all AEs recovered/resolved. No SUSARs were observed. In conclusion the combination therapy with gemcitabine and nab-paclitael did not seem to expose patients with CCA who are ineligible for ciplatinum based chemotherapy at new risks.

10 Discussion and Overall Conclusions

This clinical trial tested the combination of gemicitabine and nab-paclitaxel in patients with advanced CCA who are ineligible for the standard cisplatin-based therapy.
A total of 10 enrolled patients (ITT set) was evaluable for analysis of primary and secondary objectives. Patients of this analysis set were in median (range) 68 years old (59-70) and all patients suffered of at least one comorbidity. 60% of enrolled patients were female. The Reasons for Cisplatin ineligibility were presbycusis (N=3), chronic ischaemic heart disease with insufficieny/cardiovascular disease (N=3), thromboembolic events (N=2), chronic obstructive pulmonary disease (N=1) and ascites with contraindication for extensive hydrating (N=1). 6 (60%) patients had perihilar CCA, 2 (20%) patients had intrahepatic CCA, 1 (10%) patient had a distal CCA and 1 (10%) patient had a gallbladder cancer. All 10 patients had the histology ‘adenocarcinoma’, 90% of patients had metastases at time of enrolment. Five patients were primary resected and had a relapse or developed metastases and 5 patients had non-resectable disease or synchronous metastases. Distant metastases were located in the liver (N=3), in the lung (N=3), in lymph nodes (N=3) or in the peritoneum (N=3).

Treatment duration amounted to a median (range) time of 5.24 (03.22-9.43), months for ITT set.
A median (range) of 6 (4-12) cycles for ITT set was administered.
Median follow-up period from date of registration to death, last patient contact for patients, who were lost to follow up or to date of data lock for all patients (01. Jul. 2020) was 7.8 months for patients of ITT set.

The primary endpoint ORR amounted to 40% of ITT analysis set, which was higher than the 18.7% reported with gemcitabine and cisplatin (control arm) in the recently published TOPAZ-1 trial (Oh et al., 2022). The DCR was 80%, which was comparable to the pivotal ABC-02 trial (81.4%) and the control arm of the TOPAZ-1 trial (82.6%) with gemcitabine and cisplatin (Valle et al. 2010; Oh et al., 2022). Median PFS was 5.7 months for the ITT set which is slightly shorter than in the published ABC-02 trial with gemcitabine and cisplatin (8.0 months) but exactly comparable to the control arm with gemcitabine and cisplatin in the recently published TOPAZ-1 trial (5.7 months) (Oh et al., 2022; Valle et al., 2010). The median OS was 7.8 months for the ITT set, which was shorter than the OS with gemcitabine and cisplatin reported in the ABC-02 trial (11.7 months) or in the TOPAZ-1 trial (11.5 months). However, the NACHO trial enrolled patients, which were ineligible for cisplatin-based chemotherapy due to comorbidities as impaired renal function or significant cardiovascular diseases. These comorbidities could have affected the median OS in this frail patient population.

Analysis of safety data of this clinical trial are in line with the safety profile published in the SmPCs of the study drugs. The administration of gemcitabine and nab-paclitaxel in patients with CCA who are ineligible for cisplatin-based chemotherapy did not result in more severe side effects than in patients with metastatic pancreatic cancer (von Hoff et al., 2013).

Conclusion:
The NACHO trial suggests that gemcitabine and nab-paclitaxel as first-line treatment in patients with advanced CCA, which are ineligible for cisplatin-based chemotherapy, is safe and effective. The results of this small pilot trial warrant the conduction of a larger randomized phase II trial.

11 Tables, Graphs, and Lists Cited but not Included in the Text

11.1 Safety Data

11.1.1 Presentations of AEs

Table 27: Adverse events according to MedDRA (sorted by SOC) ITT set, N=10

AE ID	Patient ID	MedDRa-CodeCode	Preferred Term	System Organ Class level od MedDRA	NCI grade	related to IP*
3	01_01	10029354	Neutropenia	Blood and lymphatic system disorders	4	1
4	01_01	10002272	Anaemia	Blood and lymphatic system disorders	1	2
5	01_01	10024384	Leukopenia	Blood and lymphatic system disorders	4	1
8	01_01	10043554	Thrombocytopenia	Blood and lymphatic system disorders	1	1
18	01_01	10024384	Leukopenia	Blood and lymphatic system disorders	2	1
19	01_01	10029354	Neutropenia	Blood and lymphatic system disorders	3	1
41	01_02	10002272	Anaemia	Blood and lymphatic system disorders	3	2
53	01_03	10002272	Anaemia	Blood and lymphatic system disorders	1	3
54	01_03	10083158	Secondary thrombocytosis	Blood and lymphatic system disorders	n.e.	n.e.
60	01_04	10043554	Thrombocytopenia	Blood and lymphatic system disorders	2	1
62	01_04	10043554	Thrombocytopenia	Blood and lymphatic system disorders	2	1
70	01_04	10043554	Thrombocytopenia	Blood and lymphatic system disorders	1	1
79	01_05	10002272	Anaemia	Blood and lymphatic system disorders	1	3
80	01_05	10043554	Thrombocytopenia	Blood and lymphatic system disorders	2	1
87	01_05	10029354	Neutropenia	Blood and lymphatic system disorders	2	1
89	01_05	10043554	Thrombocytopenia	Blood and lymphatic system disorders	2	1
96	01_06	10043554	Thrombocytopenia	Blood and lymphatic system disorders	1	1
106	01_07	10029354	Neutropenia	Blood and lymphatic system disorders	1	1
107	01_07	10024384	Leukopenia	Blood and lymphatic system disorders	1	1
110	01_07	10043554	Thrombocytopenia	Blood and lymphatic system disorders	1	1
118	01_08	10043554	Thrombocytopenia	Blood and lymphatic system disorders	1	3

120	01_08	10029354	Neutropenia	Blood and lymphatic system disorders	n.e.	n.e.
122	01_08	10002272	Anaemia	Blood and lymphatic system disorders	3	1
123	01_08	10002272	Anaemia	Blood and lymphatic system disorders	1	1
124	01_08	10043554	Thrombocytopenia	Blood and lymphatic system disorders	1	1
129	01_08	10043554	Thrombocytopenia	Blood and lymphatic system disorders	3	1
138	01_09	10002272	Anaemia	Blood and lymphatic system disorders	3	3
143	01_10	10029354	Neutropenia	Blood and lymphatic system disorders	3	1
147	01_10	10002272	Anaemia	Blood and lymphatic system disorders	3	1
148	01_10	10043554	Thrombocytopenia	Blood and lymphatic system disorders	3	1
30	01_02	10043071	Tachycardia	Cardiac disorders	2	n.e.
1	01_01	10012727	Diarrhoea	Gastrointestinal disorders	3	4
21	01_01	10028813	Nausea	Gastrointestinal disorders	1	n.e.
22	01_02	10012727	Diarrhoea	Gastrointestinal disorders	1	2
25	01_02	10042128	Stomatitis	Gastrointestinal disorders	1	1
26	01_02	10042128	Stomatitis	Gastrointestinal disorders	2	1
31	01_02	10042128	Stomatitis	Gastrointestinal disorders	1	1
32	01_02	10042128	Stomatitis	Gastrointestinal disorders	2	1
33	01_02	10012727	Diarrhoea	Gastrointestinal disorders	2	1
36	01_02	10042128	Stomatitis	Gastrointestinal disorders	2	1
55	01_03	10028813	Nausea	Gastrointestinal disorders	2	1
56	01_03	10014542	Vomiting	Gastrointestinal disorders	2	1
57	01_03	10012727	Diarrhoea	Gastrointestinal disorders	1	1
63	01_04	10015389	Gastrooesophageal reflux disease	Gastrointestinal disorders	2	1
64	01_04	10012727	Diarrhoea	Gastrointestinal disorders	1	2
73	01_04	10012727	Diarrhoea	Gastrointestinal disorders	1	3
78	01_05	10042112	Abdominal pain upper	Gastrointestinal disorders	2	3
85	01_05	10003445	Ascites	Gastrointestinal disorders	2	3
86	01_05	10000081	Abdominal pain	Gastrointestinal disorders	2	3
88	01_05	10029932	Constipation	Gastrointestinal disorders	1	1
91	01_05	10012727	Diarrhoea	Gastrointestinal disorders	1	3
92	01_05	10000081	Abdominal pain	Gastrointestinal disorders	3	3
94	01_05	10003445	Ascites	Gastrointestinal disorders	1	3

100	01_07	10028813	Nausea	Gastrointestinal disorders	n.e.	1
101	01_07	10029932	Constipation	Gastrointestinal disorders	1	3
104	01_07	10029932	Constipation	Gastrointestinal disorders	2	3
109	01_07	10012727	Diarrhoea	Gastrointestinal disorders	1	3
111	01_07	10012727	Diarrhoea	Gastrointestinal disorders	1	3
132	01_09	10003445	Ascites	Gastrointestinal disorders	2	3
133	01_09	10028813	Nausea	Gastrointestinal disorders	3	3
134	01_09	10015389	Gastrooesophageal reflux disease	Gastrointestinal disorders	3	3
136	01_09	10000081	Abdominal pain	Gastrointestinal disorders	1	3
137	01_09	10029932	Constipation	Gastrointestinal disorders	2	3
2	01_01	10016558	Pyrexia	General disorders and administration site conditions	3	1
9	01_01	10033371	Pain	General disorders and administration site conditions	1	3
10	01_01	10014251	Oedema peripheral	General disorders and administration site conditions	1	3
20	01_01	10033371	Pain	General disorders and administration site conditions	2	3
28	01_02	10081195	General physical health deterioration	General disorders and administration site conditions	2	3
45	01_02	10002241	Generalised oedema	General disorders and administration site conditions	2	3
46	01_02	10014251	Oedema peripheral	General disorders and administration site conditions	2	3
49	01_02	10081195	General physical health deterioration	General disorders and administration site conditions	n.e.	3
50	01_02	10033371	Pain	General disorders and administration site conditions	n.e.	3
51	01_02	10033371	Pain	General disorders and administration site conditions	n.e.	n.e.
65	01_04	10028129	Mucosal inflammation	General disorders and administration site conditions	1	2

69	01_04	10016558	Pyrexia	General disorders and administration site conditions	1	3
71	01_04	10016558	Pyrexia	General disorders and administration site conditions	1	2
76	01_05	10016558	Pyrexia	General disorders and administration site conditions	n.e.	n.e.
77	01_05	10033371	Pain	General disorders and administration site conditions	n.e.	n.e.
81	01_05	10008531	Chills	General disorders and administration site conditions	2	3
93	01_05	10008531	Chills	General disorders and administration site conditions	1	3
115	01_07	10014251	Oedema peripheral	General disorders and administration site conditions	1	2
116	01_07	10014251	Oedema peripheral	General disorders and administration site conditions	1	3
117	01_08	10033371	Pain	General disorders and administration site conditions	n.e.	3
125	01_08	10014251	Oedema peripheral	General disorders and administration site conditions	1	1
126	01_08	10014251	Oedema peripheral	General disorders and administration site conditions	1	1
127	01_08	10016558	Pyrexia	General disorders and administration site conditions	1	n.e.
135	01_09	10016558	Pyrexia	General disorders and administration site conditions	1	3
140	01_10	10016558	Pyrexia	General disorders and administration site conditions	3	1
150	01_10	10014251	Oedema peripheral	General disorders and administration site conditions	2	1
151	01_10	10008531	Chills	General disorders and administration site conditions	1	1
82	01_05	10008635	Cholestasis	Hepatobiliary disorders	1	3

141	01_10	10020578	Hyperbilirubinaemia	Hepatobiliary disorders	2	1
7	01_01	10051387	Device related infection	Infections and infestations	2	3
14	01_01	10046571	Urinary tract infection	Infections and infestations	2	3
83	01_05	10028699	Onychomycosis	Infections and infestations	1	3
23	01_02	10054792	Decreased appetite	Metabolism and nutrition disorders	2	1
29	01_02	10054198	Dehydration	Metabolism and nutrition disorders	2	3
40	01_02	10020942	Hypoalbuminaemia	Metabolism and nutrition disorders	2	2
105	01_07	10002646	Decreased appetite	Metabolism and nutrition disorders	1	1
112	01_07	10002646	Decreased appetite	Metabolism and nutrition disorders	1	1
114	01_07	10002646	Decreased appetite	Metabolism and nutrition disorders	1	1
12	01_01	10076563	Peripheral sensory neuropathy	Nervous system disorders	1	1
13	01_01	10076563	Peripheral sensory neuropathy	Nervous system disorders	2	1
75	01_04	10076563	Peripheral sensory neuropathy	Nervous system disorders	3	1
90	01_05	10076563	Peripheral sensory neuropathy	Nervous system disorders	1	1
119	01_08	10076563	Peripheral sensory neuropathy	Nervous system disorders	1	1
121	01_08	10076563	Peripheral sensory neuropathy	Nervous system disorders	2	1
128	01_08	10076563	Peripheral sensory neuropathy	Nervous system disorders	3	1
144	01_10	10076563	Peripheral sensory neuropathy	Nervous system disorders	1	1
145	01_10	10076563	Peripheral sensory neuropathy	Nervous system disorders	2	1
146	01_10	10076563	Peripheral sensory neuropathy	Nervous system disorders	1	1
47	01_02	10002855	Anxiety	Psychiatric disorders	n.e.	3
52	01_02	10029412	Nightmare	Psychiatric disorders	n.e.	n.e.
152	01_10	10002855	Anxiety	Psychiatric disorders	n.e.	1

37	01_02	10013968	Dyspnoea	Respiratory, thoracic and mediastinal disorders	1	3
66	01_04	10011224	Cough	Respiratory, thoracic and mediastinal disorders	1	3
68	01_04	10011224	Cough	Respiratory, thoracic and mediastinal disorders	2	3
153	01_10	10013968	Dyspnoea	Respiratory, thoracic and mediastinal disorders	1	3
15	01_01	10081861	Anonychia	Skin and subcutaneous tissue disorders	1	1
16	01_01	10081861	Anonychia	Skin and subcutaneous tissue disorders	1	1
17	01_01	10081861	Anonychia	Skin and subcutaneous tissue disorders	1	1
24	01_02	10001760	Alopecia	Skin and subcutaneous tissue disorders	1	1
35	01_02	10011983	Decubitus ulcer	Skin and subcutaneous tissue disorders	2	3
43	01_02	10001760	Alopecia	Skin and subcutaneous tissue disorders	1	2
44	01_02	10081861	Anonychia	Skin and subcutaneous tissue disorders	2	3
48	01_02	10011983	Decubitus ulcer	Skin and subcutaneous tissue disorders	2	3
61	01_04	10001760	Alopecia	Skin and subcutaneous tissue disorders	1	1
95	01_06	10040916	Erythema	Skin and subcutaneous tissue disorders	1	1
97	01_06	10001760	Alopecia	Skin and subcutaneous tissue disorders	1	1
131	01_09	10001760	Alopecia	Skin and subcutaneous tissue disorders	1	3
139	01_10	10001760	Alopecia	Skin and subcutaneous tissue disorders	1	1
11	01_01	10057320	Peripheral venous disease	Vascular disorders	2	2
27	01_02	10019428	Haematoma	Vascular disorders	1	3
38	01_02	10021097	Hypotension	Vascular disorders	1	3
42	01_02	10021097	Hypotension	Vascular disorders	1	3
103	01_07	10043607	Thrombosis	Vascular disorders	n.e.	3
6	01_01	10021018	Hypokalemia	Electrolyte and fluid balance conditions	1	3
34	01_02	10021018	Hypokalemia	Electrolyte and fluid balance conditions	1	3
39	01_02	10021018	Hypokalemia	Electrolyte and fluid balance conditions	1	2
58	01_03	10016256	Fatigue	General disorders and administration site conditions	2	1
59	01_03	10016256	Fatigue	General disorders and administration site conditions	2	1

67	01_04	10039083	Rhinitis	Respiratory, thoracic and mediastinal disorders	1	3
72	01_04	10035664	Pneumonia	Infections and infestations	3	3
74	01_04	10035664	Pneumonia	Infections and infestations	3	3
84	01_05	10016256	Fatigue	General disorders and administration site conditions	1	1
98	01_06	10016256	Fatigue	General disorders and administration site conditions	1	3
99	01_06	10016256	Fatigue	General disorders and administration site conditions	2	3
102	01_07	10016256	Fatigue	General disorders and administration site conditions	1	3
108	01_07	10016256	Fatigue	General disorders and administration site conditions	1	1
113	01_07	10016256	Fatigue	General disorders and administration site conditions	2	1
130	01_09	10016256	Fatigue	General disorders and administration site conditions	1	3
142	01_10	10016256	Fatigue	General disorders and administration site conditions	2	1
149	01_10	10016256	Fatigue	General disorders and administration site conditions	2	1

*1:related; 2:possible related; 3: not related; 4: not evaluated
n.e.:not evaluated

11.1.2 Narratives of Deaths, SAEs, Other Significant AEs

Not applicable.

12 List of References

1. Abraham SC, Lee JH, Hruban RH, Argani P, Furth EE, Wu TT. Molecular and immunohistochemical analysis of intraductal papillary neoplasms of the biliary tract. Hum Pathol. 2003;34:902-10.
2. Cox DR: Regression models and life tables. J Roy Stat Soc (B) 1972; 34: 187-202
3. Gandou C, Harada K, Sato Y, Igarashi S, Sasaki M, Ikeda H, Nakanuma Y. Hilar cholangiocarcinoma and pancreatic ductal adenocarcinoma share similar histopathologies, immunophenotypes, and development-related molecules. Hum Pathol. 2013;44:811-21
4. Glimelius B, Hoffman K, Sjödén PO, Jacobsson G, Sellström H, Enander LK, Linné T, Svensson C. Chemotherapy improves survival and quality of life in advanced pancreatic and biliary cancer. Ann Oncol. 1996;7:593-600
5. Goldstein D, Hassan El-Maraghi R, Hammel P, Heinemann V, Kunzmann V, Sastre J, Scheithauer W, Siena S, Tabernero J, Teixeira L, Tortora G, Van Laethem J-L, Young R, Penenberg DN, Lu B, Romano A, Von Hoff DD. *nab*-Paclitaxel Plus Gemcitabine for Metastatic Pancreatic Cancer: Long-Term Survival From a Phase III Trial. JNCI. 2015; 1-10
6. Hulley, S.B., Cummings, T.B., Browner, W.S., Cum-mings, S.R., Hulley, D.G., & Hearst, N. (2001).Designing clinical research: An epidemiologicalapproach. Philadelphia: Lippincott, Williams, &Wilkins
7. Hezel AF, Zhu AX. Systemic therapy for biliary tract cancers. Oncologist. 2008;13:415-23.
8. Kaplan EL, Meier P. Nonparametric estimation from incomplete observations. J Am Stat Ass 1958; 53: 457-481
9. Kubicka S: Cholangiozelluläres Karzinom und Gallenblasenkaerzinom. Z Gastroenterol 2004; 42: 397-402
10. Lackey, N.R., & Wingate, A.L. (1998). The pilot study: One key to research success. In P.J. Brink & M.J.Wood (Eds.), Advanced design in nursing research(2nd ed.). Thousand Oaks, CA: Sage
11. Lancaster GA, Dodd S, Williamson PR. Design and analysis of pilot studies: recommendations for good practice. J Eval Clin Pract. 2004;10:307-12.
12. Nieswiadomy, R.M. (2002). Foundations of nursingresearch (4th ed.). Upper Saddle River, NJ: PearsonEducation.
13. Oh D-Y, He AR, Qin S, Chen L-T, Okusaka T, Vogel A, Kim JW, et al. A phase 3 randomized, double-blind, placebo-controlled study of durvalumab in combination with gemcitabine plus cisplatin (GemCis) in patients (pts) with advanced biliary tract cancer (BTC): TOPAZ-1. NEJM Evid 2022; 1
14. Okuda K, Nakanuma Y, Miyazaki M. Cholangiocarcinoma: recent progress. Part 2: molecular pathology and treatment. J Gastroenterol Hepatol. 2002;17:1056-63. Review.

15. Okusaka T, Nakachi K, Fukutomi A, Mizuno N, Ohkawa S, Funakoshi A, Nagino M, Kondo S, Nagaoka S, Funai J, Koshiji M, Nambu Y, Furuse J, Miyazaki M, Nimura Y. Gemcitabine alone or in combination with cisplatin in patients with biliary tract cancer: a comparative multicentre study in Japan. Br J Cancer. 2010;103:469-74.
16. Razumilava N, Gores GJ. Cholangiocarcinoma. Lancet. 2014;383:2168-79.
17. Rizvi S, Gores GJ. Pathogenesis, diagnosis, and management of cholangiocarcinoma. Gastroenterology. 2013;145(6):1215-29.
18. Rizvi S, Gores GJ. Molecular pathogenesis of cholangiocarcinoma. Dig Dis. 2014;32:564-9.
19. Sato Y, Harada K, Sasaki M, Nakanuma Y. Histological Characterization of Biliary Intraepithelial Neoplasia with respect to Pancreatic Intraepithelial Neoplasia. Int J Hepatol. 2014;2014:678260.
20. Valle J, Wasan H, Palmer DH, Cunningham D, Anthoney A, Maraveyas A, Madhusudan S, Iveson T, Hughes S, Pereira SP, Roughton M, Bridgewater J; ABC-02 Trial Investigators. Cisplatin plus gemcitabine versus gemcitabine for biliary tract cancer. N Engl J Med. 2010;362:1273-81.
21. Valle JW, Furuse J, Jitlal M, Beare S, Mizuno N, Wasan H, Bridgewater J, Okusaka T. Cisplatin and gemcitabine for advanced biliary tract cancer: a meta-analysis of two randomised trials. Ann Oncol. 2014;25:391-8.
22. Von Hoff DD, Ramanathan RK, Borad MJ, et al. Gemcitabine plus nab-paclitaxel is an active regimen in patients with advanced pancreatic cancer: a phase I/II trial. J Clin Oncol 2011;29:4548-54.
23. Von Hoff DD, Ervin T, Arena FP, Chiorean EG, Infante J, Moore M, Seay T, Tjulandin SA, Ma WW, Saleh MN, Harris M, Reni M, Dowden S, Laheru D, Bahary N, Ramanathan RK, Tabernero J, Hidalgo M, Goldstein D, Van Cutsem E, Wei X, Iglesias J, Renschler MF. Increased survival in pancreatic cancer with nab-paclitaxel plus gemcitabine. N Engl J Med. 2013;369:1691-703.

13 Appendices

13.1 Study Information (stand alone documents, will be available upon request)

13.1.1 Study Protocol

13.1.2 Sample eCRF

13.1.3 Ethic votum

13.1.4 Sample Patient Information Sheet and Informed Consent Form

13.1.5 List of Signatures of the *LKP* [National Coordinating Investigator] and the Sponsor

By signing this Clinical Study Report, the undersigned authors agree with the contents of this Clinical Study Report. The clinical trial reported here was conducted in accordance with the principles of the Declaration of Helsinki, Good Clinical Practice (GCP), and applicable legislation.

Sponsor (Representative)

Prof. Dr. Stefan Kasper-Virchow	Essen, 30.07.2022
	Place, date

National Coordinating Investigator / Investigator

Prof. Dr. Stefan Kasper-Virchow	Essen, 30.07.2022
	Place, date