NAB-PACLITAXEL PLUS GEMCITABINE VERSUS GEMCITABINE FOR THE FIRST LINE TREATMENT OF METASTATIC OR LOCALLY ADVANCED UNRESECTABLE ADENOCARCINOMA OF THE PANCREAS: A PHASE II RANDOMIZED STUDY

PROTOCOL VERSION DATED: 07 January 2014

EudraCT: 2013-004180-32

Protocol No: AX-PANC-SY001

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This clinical study will be conducted in accordance with International Conference on Harmonization (ICH) Good Clinical Practices (GCP) Guidelines

CONFIDENTIAL

Investigator-Initiated Trial Protocol

Study title: Nab-paclitaxel plus gemcitabine versus gemcitabine for the first line treatment of metastatic or locally advanced unresectable adenocarcinoma of the pancreas: A Phase II randomized study	
Phase	**II**
Kind of study **(interventional, non-interventional or pre-clinical):**	Interventional
Indication	Metastatic or unresectable locally advanced pancreatic cancer
Rationale	Pancreatic cancer is responsible for 38,000 deaths per year, and is the fourth most common cause of death from cancer in both sexes combined, a position relatively high when compared to incidence (tenth position) because of the very poor prognosis (the M/I ratio is 98%) (Siegel et al, 2013). The incidence of pancreatic carcinoma has increased almost 300% since 1950 and now exceeds the incidence of stomach cancer. Carcinoma of the exocrine pancreas is nearly always a fatal disease. The overall 5-year survival rate for the disease is approximately 4%. Locally advanced or metastatic pancreatic cancer is relatively unresponsive to chemotherapy. Gemcitabine therapy provides some benefit and modestly improves survival compared with fluorouracil, but median survival in patients with advanced disease remains less than 6 months (Burris, 1997). Until recently, cytotoxic drug combinations were not able to show survival advantage compared to Gemcitabine alone in numerous randomized phase III studies. Randomized phase III Prodige trial evaluated FOLFIRINOX regimen in metastatic pancreatic cancer patients (Conroy et al, 2011). Both median progression-free survival (PFS) (6.4 vs 3.3 months, p<0.001) and median overall survival (OS) (11.1 vs 6.8 months, p<0.001) were dramatically improved. In patients with good performance status FOLFIRINOX remains a viable first-line option. However, toxicity of FOLFIRINOX regimen still remains a concern. The effect of FOLFIRINOX on quality of life (QoL) in metastatic pancreatic cancer was analyzed from the PRODIGE 4/ACCORD 11 trial. FOLFIRINOX combination was found to

	significantly reduce QoL impairment compared with single-agent gemcitabine. Baseline QoL scores improved estimation of survival probability when added to baseline clinical and demographic variables. Nab-paclitaxel is an albumin-bound nanoparticle form of paclitaxel. In a recent phase III study of Metastatic Pancreatic Adenocarcinoma Clinical Trial (MPACT) including 861 patients, patients were randomly assigned to 1 of 2 regimens: nab-paclitaxel 125 mg/m² followed by gemcitabine 1000 mg/m² for 3 weeks, then a week of rest; or gemcitabine 1000 mg/m² administered weekly for 7 weeks, then a week of rest, followed by cycles of weekly gemcitabine administration for 3 weeks and a week of rest (von Hoff et al, 2013). OS was improved significantly with nab-paclitaxel + gemcitabine combination compared to gemcitabine alone (median, 8.5 vs. 6.7 months; hazard ratio [HR], 0.72; *P* = .000015). These improvements suggest a 31% reduction in the risk of progression or death. At 12 months, the survival rate was 35% with the combination versus 22% with gemcitabine alone, translating into a 59% increase in survival (p = 0.00020). In addition to OS, the *nab*-paclitaxel combination surpassed gemcitabine alone for median PFS (5.5 vs. 3.7 months; HR: 0.69; p = 0.000024) and the overall response rate (23% vs. 7%).The toxicity of the combination was modest and easily manageable. This combination may represent a new standard in the management of these patients. QoL changes in patients receiving nab-paclitaxel in combination with gemcitabine for the first-line treatment of metastatic or locally advanced unresectable pancreatic carcinoma have not been explored. This randomized, phase II study analyzes the effect of nab-paclitaxel plus gemcitabine on QoL of these patients. Efficacy and safety of the combination will also be analyzed.
Study objectives	
	<u>Primary objectives:</u> **3-months deterioration-free rate (percentage of patients free from definitive deterioration)** EORTC QLQ-C30 (validated version for Turkish using a reduction of at least 10 points as a meaningful clinical difference) will be used to calculate “time until definitive deterioration” (TUDD) and compare patients receiving first-line Nab-Paclitaxel plus Gemcitabine versus first-line gemcitabine for metastatic or locally advanced unresectable adenocarcinoma of

	the pancreas. EORTC QLQ-C30 scores will be calculated every four weeks following the EORTC QLQ-C30 recommendations for calculations and scoring (EORTC QLQ-C30 published manual).
	<u>Secondary objectives:</u> Overall survival (OS) Progression-free survival (PFS) Response rate Safety and toxicity Predictive and prognostic factors: Serum and archived tumor tissue biomarkers (available patients) for prognosis and prediction to response to treatment and toxicity.
Study design	This is a randomized, multicenter, phase II study of with nab-paclitaxel plus gemcitabine or gemcitabine alone for the treatment of chemotherapy-naïve patients with locally advanced or metastatic pancreatic cancer. Arm 1: Nab-paclitaxel plus gemcitabine Arm 2: Gemcitabine alone
Study Duration:	The first patient is planned to be enrolled in March 2014. The recruitment period is estimated to be around 14 months. Patients will receive study treatment until death, disease progression (PD), occurrence of intolerable side effects, or withdrawal of consent, whichever comes first. All patients will be followed for survival. A patient is considered “Discontinued from Study Follow-up” only if study treatment has been discontinued **AND** one of the following occurs: a. Patient withdraws consent. b. Patient is lost to follow-up. c. Patient dies. d. Patient completes 1-year follow-up. e. Study is completed or terminated by the Sponsor.
Patient	Chemotherapy-naïve patients presenting with unresectable locally advanced or metastatic

population	pancreatic adenocarcinoma and a measurable disease by RECIST.
Inclusion criteria:	1. Patients presenting with metastatic or unresectable pancreatic adenocarcinoma and with no prior chemotherapy 2. Patients with a measurable/evaluable disease by RECIST 3. Age ≥ 18 years 4. ECOG performance status 0 or 1 5. Patients with signed informed consent form 6. Patients with adequate bone marrow function: granulocyte count ≥1500 and platelet count ≥100,000 per cubic milimeter. 7. Patients with adequate liver function defined as: a. Total bilirubin <2 mg/dl b. ALP/GGT <5x upper normal limit (ULN) c. ALT/AST <2.5x upper normal limit (ULN)
Exclusion criteria:	1. Any prior systemic or investigational therapy for metastatic pancreatic cancer. Systemic therapy administered alone or in combination with radiation in the adjuvant setting is permitted if it is completed > 6 months prior to the time of study enrollment. 2. Inability to comply with study and/or follow-up procedures. 3. Presence of significant comorbidity including clinically significant cardiac disease (e.g. congestive heart failure, symptomatic coronary artery disease and cardiac arrhythmias not well controlled with medication) or myocardial infarction within the last 12 months and any other major organ failure. 4. Presence of any condition that, in the opinion of the investigator, renders the subject at high risk from treatment complications or might affect the interpretation of the results of the study. 5. Presence of central nervous system or brain metastases. 6. Life expectancy < 12 weeks. 7. Pregnancy (positive pregnancy test) or lactation. 8. Prior malignancy except for adequately treated basal cell skin cancer, in situ cervical

	cancer, adequately treated Stage I or II cancer from which the patient is currently in complete remission, or any other form of cancer from which the patient has been disease-free for 5 years. 9. Lack of physical integrity of the upper gastrointestinal tract or malabsorption syndrome. 10. Known, existing uncontrolled coagulopathy. 11. Pre-existing sensory neuropathy > grade 1. 12. Major surgery within 4 weeks of the start of study treatment, without complete recovery. 13. Concurrent/pre-existing use of coumadin. 14. Patients older than 76 years of age. 15. Patients with active infection. 16. Patients with chronic diarrhea.
Treatment regimen	**Arm 1:** Nab-paclitaxel 125 mg/m2 as 30- to 40-minute infusion (maximum infusion time not to exceed 40 minutes) once weekly for 3 weeks followed by a week of rest. plus Gemcitabine 1000 mg/m2 as a 30- to 40-minute infusion (maximum 40 minutes) once weekly for 3 weeks followed by a week of rest. OR **Arm 2:** Gemcitabine 1000 mg/m2 as a 30- to 40-minute infusion (maximum 40 minutes) administered weekly for 7 weeks followed by a week of rest (8-week cycle; cycle 1 only), followed by cycles of weekly administration for 3 weeks (on days 1, 8, and 15) followed by one week of rest (4-week cycle). All patients will be considered for available second-line therapies or best supportive care on the discretion of the investigators.
Dose modification plan:	Rules for Dose Omissions and Modified Schedules Day 1 dose missed; If the dose held or missed was to be given on Day 1 of the next cycle, that next cycle will

not be considered to start until the day the first dose is actually administered to the patient (ie, 1-2-3-Rest, X-1-2-3-Rest, etc).

Day 8 dose is missed;

Cycle continues per protocol, with one dose not given (ie, 1-2-3-Rest, 1-X-3-Rest, 1-2-3-Rest, etc). Day 15 is administered as per cycle calendar if counts and chemistries permit.

Day 15 dose missed;

That week becomes the week of rest. Next dose (if counts and chemistries permit) becomes Day 1 of a new cycle, and the patient is considered to have had a x2q3 (21-day) cycle (ie, 1-2-3-Rest, 1-2-X, 1-2-3-Rest, etc).

The maximum delay: The maximum delay between a missed scheduled dose and the next one (whichever dose was missed) should not be longer than 21 days (except for peripheral neuropathy)

Two dose modifications are permitted. If a toxicity requiring dose modification occurs following the second dose reduction of either drug, further treatment should be discontinued.

Dose Modifications;

Dose Level	**Nab-Paclitaxel Dose (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 Tables 2-4 for specific recommendations regarding dose reductions.

b) A maximum of 2 dose-level reductions are allowed.

Patients experiencing study drug-related toxicities that require a delay in scheduled nab-paclitaxel or gemcitabine dosing for ≥21 days will be discontinued from further treatment in

this study (except for peripheral neuropathy). When a dose reduction is required, no dose re-escalation will be permitted for the duration of study treatment.

DOSE MODIFICATIONS AT DAY 1;

In the event dose modifications are required at the beginning of a cycle due to AEs or hematologic toxicities, doses of nab-paclitaxel and gemcitabine may be adjusted

Dose Modifications for Day 1 of Each Cycle (Hematologic Toxicity);

Treatment day counts and toxicity

ANC	**Platelets**		**Timing**
≥1.5 x 109/L	And	≥100 x 109/L	Treat on time
<1.5 x 109/L	Or	<100 x 109/L	Delay by 1 week intervals until recovery

Dose Modifications for Day 1 of Each Cycle (Non-Hematologic Toxicity)

Non Hematologic Toxicity and/or Dose Hold with Previous Cycle	
Toxicity/dose held	**Gemcitabine/Gemcitabine+Nab-paclitaxel dose this cycle**
Grade 0, 1 or 2 toxicity	Same as Day 1 previous cycle (except for cutaneous toxicity)
Grade 3 toxicity	Decrease gemcitabine and nab-paclitaxel to next lower dose level
Grade 4 toxicity	Off protocol treatment
Dose held in 2 previous consecutive cycles	Decrease gemcitabine to next lower dose level and continue throughout the rest of treatment

a) If the toxicity only affects neuropathy, then only nab-paclitaxel should be reduced

b) Pulmonary embolism (a Grade 4 toxicity in the CTCAE tables) if mild or asymptomatic, will be exempt from this requirement.

Gemcitabine and nab-paclitaxel or gemcitabine monotherapy will be provided within the

	study protocol until patients progress or are unable to tolerate the treatment. Patients on single-agent gemcitabine arm will be allowed cross-over to the combination arm in case of a definitive deterioration in the GHS score of at least 10 points.
Endpoints:	**<u>Primary endpoint:</u>** **3-months deterioration-free rate (percentage of patients free from definitive deterioration).** Quality of life (QoL): EORTC QLQ-C30 (validated version for Turkish using a reduction of at least 10 points as a meaningful clinical difference) will be used to calculate "time until definitive deterioration" (TUDD) and compare patients receiving first-line Nab-Paclitaxel plus Gemcitabine versus first-line gemcitabine for metastatic or locally advanced unresectable adenocarcinoma of the pancreas. **<u>Secondary</u>** Overall survival (OS) Progression-free survival (PFS) Overall Response Rate (ORR) Safety and toxicity Predictive and prognostic factors: Serum and archived tumor tissue biomarkers (available patients) for prognosis and prediction to response to treatment and toxicity.
Statistical plan	**Rationale and Methodology:** The objective of the trial is to compare QoL in patients receiving Nab-paclitaxel plus gemcitabine versus gemcitabine. QoL will be assessed using the EORTC QLQ-C30 for at least 12 months (in those who are still alive) for all patients (even if they deteriorate 10 points and meet the study end point). Sample size calculations will be based on the GHS score considering a 10-point minimal clinically important difference. A definitive deterioration is considered when the score decreases by more than 10 points as compared to baseline. Thus, "time until definitive deterioration" (TUDD) is defined as the time from randomization to the first observation of a definitive deterioration of the score. The hypotheses for sample size calculations are based on the results of the article "Impact

	of FOLFIRINOX compared with gemcitabine on quality of life in patients with metastatic pancreatic cancer: results from the PRODIGE/ACCORD 11 randomized trial", published in Journal of Clinical Oncology. The curves of TUDD comparing FOLFIRINOX and gemcitabine show that the percentages of patients free from definitive deterioration at 3-months are 83% in the FOLFIRINOX arm and 69% in the gemcitabine arm. Assuming the same for Nab-Paclitaxel plus Gemcitabine arm, these percentages are used as hypotheses for sample size calculations. So, a 3-month deterioration-free rate of 83% for Nab-Paclitaxel plus Gemcitabine arm and 69% for gemcitabine arm will be assumed for calculating the sample size using a log-rank test. Primary end-point will be 3-months deterioration-free rate (percentage of patients free from definitive deterioration as defined above). Sample size calculations: • Hypotheses a. 2-sided alpha=0.05 b. power=80% c. accrual 7 pts per month d. 3-month deterioration-free rate of 83% for Nab-Paclitaxel plus Gemcitabine e. 3-month deterioration-free rate of 69% for gemcitabine arm • Results a. Accrual duration 14 months b. Total study duration 21 months c. Total sample size n=100 d. Number of events E=68 (number of patients with deteriorations). Accounting for a 20% missing or incomplete forms, the total sample size will be n=125.

THERAPY SYNOPSIS		**NAME, SURNAME** Birthday -- -- ---- STID ---		
	DAY	**WEEK**	**NABPACLITAX**	**GEMCITABINE**
CT/ MRI (SCREENING)				**QoL**
APPLICATION WEEKLY: <u>Nab-paclitaxel</u> 125 mg/m2 Plus <u>Gem</u> 1000 mg/m2 (3 weeks on, 1 week off) **OR** <u>Gem</u> 1000 mg/m2 iv 30'	**1**	**1**		
	8	**2**		
	15	**3**		
	22	**4**	**REST**	
	29	**5**		
	36	**6**		**QoL**
	43	**7**		
CT / MRI (FOLLOW UP # 1)	**50-56**	**8**	**PD: OFF STUDY SD/PR/CR: FURTHER THERAPY**	
APPLICATION WEEKLY: <u>Nab-paclitaxel</u> 125 mg/m2 Plus <u>Gem</u> 1000 mg/m2 (3 weeks on, 1 week off) **OR** <u>Gem</u> 1000 mg/m2 iv 30'	**57**	**9**		
	64	**10**		
	71	**11**		
	78	**12**	**REST**	
	85	**13**		
	92	**14**		**QoL**
	99	**15**		
CT / MRI (FOLLOW UP # 2)	**106-112**	**16**	**PD: OFF STUDY SD/PR/CR: FURTHER THERAPY**	
APPLICATION WEEKLY: (see above, CT/ MRI follow up every 7-8 weeks)	**113**	**17**		
	120	**18**		
	127	**19**		
	134	**20**	**REST**	

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ABBREVIATIONS AND DEFINITIONS OF TERMS

AE	Adverse Event
ALT	Alanine Aminotransferase (SGPT)
ASCO	American Society of Clinical Oncology
AST	Aspartate Aminotransferase (SGOT)
β-HCG	Beta Human Chorionic Gonadotrophin
BSA	Body Surface Area
BUN	Blood Urea Nitrogen
CA	Cyanuric Acid, Carbohydrate Antigen
CBC	Complete blood chemistry
CFR	Code of Federal Regulations
CR	Complete Response
CrCl	Creatinine Clearance
CRF	Case Report Form
CRO	Contract Research Organization
CT	Computed Tomography
CTC	Common Toxicity Criteria
CTCAE	Common Toxicity Criteria For Adverse Events
CXR	Chest X-ray
CYP2A6	Cytochrome P-450 Drug Metabolizing Enzyme 2A6
DAR	Drug Accountability Record
DCR	Disease Control Rate
DLT	Dose Limiting Toxicity
DR	Duration of Response
ECG	Electrocardiogram
EORTC	European Organization for Research and Treatment of Cancer
EU	Europe
F	Fahrenheit
FDA	Food and Drug Administration
GCP	Good Clinical Practices
G-CSF	Granulocyte Colony-stimulating Factor
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Conference on Harmonisation

IEC	Independent Ethics Committee
IND	Investigational New Drug
IRB	Institutional Review Board
IU	International Units
KPS	Karnofsky Performance Status
LDH	Lactic Dehydrogenase
MRI	Magnetic Resonance Imaging
MTD	Maximum Tolerated Dose
NCI	National Cancer Institute
Ng	Nanogram(s)
NYHA	New York Heart Association
ORR	Overall Tumor Response Rate
OS	Overall Survival
PD	Progressive Disease, Disease Progression
PR	Partial Response
PT	Prothrombin Time
QoL	Quality of Life
RBC	Red Blood Cell
RECIST	Response Evaluation Criteria in Solid Tumors
SAE	Serious Adverse Event
SD	Stable Disease; Standard Deviation
SOP	Standard Operating Procedure
TTP	Time to Tumor Progression
TUDD	Time until definitive deterioration
ULN	Upper Limit of Normal
US	Ultrasound
USA	United States of America
WBC	White Blood Cell
WHO	World Health Organization

Signature page

Principal investigator	Prof. Suayib Yalcin	_____ Location, date _____ Signature
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1. INTRODUCTION AND STUDY RATIONALE

1.1. Background

Pancreatic cancer is responsible for 38,000 deaths per year, and is the fourth most common cause of death from cancer in both sexes combined, a position relatively high when compared to incidence (tenth position) because of the very poor prognosis (the M/I ratio is 98%) (Siegel R et al, 2013). This number represents 27% of all deaths from gastrointestinal malignancy in the United States. The annual incidence of pancreatic cancer in the Surveillance, Epidemiology, and End Results (SEER) database for the USA is 8.9 cases per 100,000. The incidence of pancreatic carcinoma has increased almost 300% since 1950 and now exceeds the incidence of stomach cancer and cancer of the rectum (Benarde MA et al, 1977; Mack TM et al, 1981). Carcinoma of the exocrine pancreas is nearly always a fatal disease. The overall 5-year survival rate for the disease is approximately 4% (SEER Cancer Statistics Review 1973-1996).

Complete tumor resection is the only treatment with a chance of cure but only feasible in 5-15% of patients. Despite curative resection, median survival does not exceed 12-18 months. After 2 years, 20-35% of the patients remain alive, after 5 years 5-10% of patients. About 30-40% of patients have locally advanced disease. Median survival of these patients is 3-8 months without further treatment. However, about 70% of all patients present with disseminated disease at the first diagnosis or with relapse after curative resection. Median survival for these patients is 3-5 months.

At the University of Chicago, the 3-year survival rate of 912 patients with pancreatic cancer was only 2.5% (Connolly MM et al, 1987). At the Memorial Sloan-Kettering Cancer Center, only 18% of patients were eligible for a potantially curative resection, with a 30-day operative mortality rate of 3.4%. The actuarial 5-year survival rate in patients who did not undergo resection was 0%, compared with 24% in patients who underwent resection (Geer RJ et al, 1993).

The patterns of failure after potentially curative resection include local relapse and metastatic involvement of the liver or peritoneal cavity. In one study of 36 patients, 19% experienced local failure only, whereas 73% had distant and local failure (Griffin JF et al, 1990). The most common sites of failure were in the liver (62%) and peritoneal cavity (42%).

In chemotherapy and radiation therapy trials, the most important factor that has consistently been of greatest prognostic importance is the performance status of the patient: The better the level of performance, the better the response rate or survival rate, or both.

Using traditional criteria of antitumor response, advanced adenocarcinoma of the pancreas rarely responds to single-agent chemotherapy. In clinical studies, single-agent chemotherapy generally does not reach response rates (complete or partial response) of 20% using WHO criteria. Response rates are usually below 15% (Burris HA, 2005; Heinemann V et al, 2006).

This is also true for treatment with the nucleoside analogue gemcitabine which showed response rates of about 11% in locally advanced or metastatic pancreatic cancer patients (Casper ES et al, 1994). There is considerable interest, however, in its use as a single agent or as a component of combination chemotherapy because of a randomized trial conducted by Burris and coworkers (Burris HA et al, 1997). These investigators randomized patients to receive either Gemcitabine or 5-FU. End points were survival and a nontraditional benefit criterion called “clinical benefit response”, defined as a composite of pain control, Karnofsky performance status, and weight. Gemcitabine achieved a clinical benefit response in 24% of patients, whereas 5-FU achieved benefit in only 5% of the patients (p=0.0022). Survival was also improved for Gemcitabine (median survival, 5.6 months) compared to 5-FU (median survival 4.4 months) (p=0.0025). Largely as a result of this study, Gemcitabine has been marketed for palliative treatment of advanced pancreatic cancer. Despite the apparent, although modest, activity of gemcitabine in the treatment of advanced pancreatic cancer, the use of gemcitabine in combination with other agents has been disappointing until recently, achieving modest responses (Hidalgo M et al, 1999; Berlin JD et al, 2002; Rocha-Lima CM et al, 2006; Ueno H et al, 2007; Kulke MH et al, 2009).

Randomized phase III Prodige trial evaluated FOLFIRINOX regimen in metastatic pancreatic cancer patients (Conroy et al, 2011). Both median progression-free survival (PFS) (6.4 vs 3.3 months, p<0.001) and median overall survival (OS) (11.1 vs 6.8 months, p<0.001) were dramatically improved. In patients with good performance status FOLFIRINOX remains a viable first-line option. However, toxicity of FOLFIRINOX regimen still remains a concern.

The effect of FOLFIRINOX on QoL in metastatic pancreatic cancer was analyzed from the PRODIGE 4/ACCORD 11 trial (Gourgou-Bourgade S et al, 2013). Time until definitive deterioration ≥20 points was significantly longer for FOLFIRINOX combination compared to gemcitabine alone for global health status, physical, role, cognitive, and social functioning, and six symptom domains (fatigue, nausea/vomiting, pain, dyspnea, anorexia and constipation). Physical functioning, constipation and dyspnea were independent significant prognostic factors for survival with treat ment arm, age older than 65 years, and low serum albumin. FOLFIRINOX combination was found to significantly reduce QoL impairment compared with single-agent gemcitabine. Baseline QoL scores improved estimation of survival probability when added to baseline clinical and demographic variables (Gourgou-Bourgade S et al, 2013).

1.2. Nab-paclitaxel

Nab-paclitaxel is an albumin-bound nanoparticle form of paclitaxel. Nab-paclitaxel is a novel formulation of paclitaxel that does not require solvents such as polyoxyethylated castor oil (Cremophor EL®: CrEL) and ethanol. Use of these solvents has been associated with toxic response, including hypersensitivity reactions and prolonged sensory neuropathy, as well as a negative impact in relation to the therapeutic index of paclitaxel. Use of nab-paclitaxel can potentially avoid these limitations. Consequently, nab-paclitaxel displays greater antitumor activity and less toxicity than solvent-base paclitaxel.

Nab-paclitaxel is prepared by high-pressure homogenization of paclitaxel in the presence of serum albumin, resulting in a colloidal suspension comprising nanoparticles of 130 nm on average, which prevent the risk of capillary blockage after intravenous infusion (Desai et al, 2006). Nab-paclitaxel consists of a lyophilized powder, which is reconstituted with 20 mL 0.9% sodium chloride solution before intravenous infusion. Each single-use vial contains 100 mg of paclitaxel and approximately 900 mg of human albumin. The final colloid solution contains 5 mg/mL of paclitaxel and approximately 45 mg/mL of albumin. Based upon in vivo study, it seems that the nab particles disperse into the individual albumin molecules with bound paclitaxel immediately after introduction into aqueous solution, as would occur after injection into the bloodstream (Gradishar, 2006).

1.3. Nab-paclitaxel preclinical studies

In athymic mice bearing human cancer xenografts, the antitumor activity and toxicity profile of nab-paclitaxel was better than that of CrEL- paclitaxel (Desai et al, 2006). The lethal dose (LD)50 and maximum tolerated dose (MTD) for nab-paclitaxel and CrEL-paclitaxel were 47 and 30 mg/kg/day and 30 and 13.4 mg/kg/day, respectively. At equitoxic doses, nab-paclitaxel had significantly better antitumor effects including tumor-free survival, time to tumor recurrence (P = 0.004), tumor doubling time (P = 0.0015), and tumor volume (P = 0.009) compared with CrEL-paclitaxel. At an equal dose of paclitaxel, the level of intratumoral paclitaxel accumulation was higher in nab-paclitaxel-treated mice than those in receipt of CrEL-paclitaxel. The extent of endothelial binding and transcytosis of paclitaxel was significantly greater for nab-paclitaxel than CrEL-paclitaxel. These findings indicated that nab-paclitaxel mediates greater intratumoral accumulation of paclitaxel and associated increased efficacy compared with CrEL-paclitaxel.

1.4. Nab-paclitaxel pharmacokinetics

In a phase I study of nab-paclitaxel administration over 30 minutes every 3 weeks in 19 patients with metastatic melanoma or breast cancer, the MTD was determined to be 300 mg/m^2 (Ibrahim et al, 2002). Plasma levels of paclitaxel declined in a biphasic manner after intravenous administration of nab-paclitaxel with a rapid first phase representing distribution to the peripheral tissue and the second slower phase representative of drug elimination.

In another pharmacokinetic study, nab-paclitaxel (260 mg/m^2 given as a 30-minute infusion) was compared with CrEL-paclitaxel (175 mg/m^2 given as a 180-minute infusion) (Gardner et al, 2008). The mean fraction unbound of paclitaxel was significantly higher for nab-paclitaxel than CrEL-paclitaxel (0.063 ± 0.021 vs 0.024 ± 0.009; P < 0.001), although the total drug exposure was comparable between the two drug formulations. These findings are in agreement with the greater antitumor efficacy of nab-paclitaxel compared with that of CrEL-paclitaxel.

1.5. Nab-paclitaxel in metastatic breast cancer

Nab-paclitaxel is widely approved for the treatment of metastatic breast cancer on the basis of results from pivotal trials showing that it has superior antitumor effects and improved tolerability than solvent-based paclitaxel (Gradishar et al, 2005). Forty-six

patients were randomized to nabpaclitaxel (260 mg/m^2 over a 30-minute infusion) without premedication or CrEL-paclitaxel (175 mg/m^2 over a 3-hour infusion) with standard premedication. Inclusion criteria included no receipt of taxane for metastatic disease and no relapse with metastatic disease within 1 year of adjuvant taxane therapy. The objective response rate (ORR) and median time to progression (TTP) were significantly higher in nab-paclitaxel-treated patients than those receiving CrEL-paclitaxel (ORR: nab-paclitaxel 33% vs CrEL-paclitaxel 19%; *P* = 0.001, TTP: nab-paclitaxel 23.0 weeks vs CrEL-paclitaxel 16.9 weeks; hazard ratio [HR] = 0.75, *P* = 0.001). Maximum responses occurred by cycle 3 in 91% of responders in the nab-paclitaxel group and in 81% of responders in the CrEL-paclitaxel group. The OS in the nab-paclitaxel group was greater than that in CrEL-paclitaxel group (65.0 weeks vs 55.7 weeks, respectively), but this did not reach statistical significance (*P* = 0.374). This trial showed that nab-paclitaxel has superior clinical benefit including greater efficacy and a favorable safety profile without premedication compared with CrEL-paclitaxel.

1.6. Nab-paclitaxel in metastatic pancreatic cancer

Initial phase I/II study showed substantial antitumor activity of gemcitabine/nab-paclitaxel combination in metastatic pancreatic cancer (Von Hoff et al, 2011). The schedule was as follows: gemcitabine 1000 mg/m^2 and nab-paclitaxel at 125 mg/m^2 doses weekly for three doses in a 4 week schedule. A 48% response rate was achieved at MTD , with 12.2 median months of overall survival and 48% 1-year survival. Interestingly, preclinical part of the same study showed increased intratumoral concentration of gemcitabine by 2.8-fold in mice receiving *nab*-paclitaxel plus gemcitabine versus those receiving gemcitabine alone.

This study was followed by a phase III study of Metastatic Pancreatic Adenocarcinoma Clinical Trial (MPACT) (Von Hoff et al, 2013). A total of 861 patients were randomly assigned to 1 of 2 regimens: nab-paclitaxel 125 mg/m² followed by gemcitabine 1000 mg/m² for 3 weeks, then a week of rest; or gemcitabine 1000 mg/m² administered weekly for 7 weeks, then a week of rest, followed by cycles of weekly gemcitabine administration for 3 weeks and a week of rest (von Hoff et al, 2013). OS was improved significantly with nab-paclitaxel + gemcitabine combination compared to gemcitabine alone (median, 8.5 vs. 6.7 months; hazard ratio [HR], 0.72; *P* = .000015). These improvements suggest a 31% reduction in the risk of progression or death. At 12 months, the survival rate was 35% with the combination versus 22% with gemcitabine

alone, translating into a 59% increase in survival (p = 0.00020). In addition to OS, the *nab*-paclitaxel combination surpassed gemcitabine alone for median PFS (5.5 vs. 3.7 months; HR: 0.69; p = 0.000024) and the overall response rate (23% vs. 7%).The toxicity of the combination was modest and easily manageable.

1.7. Toxicity

In the pivotal, randomized phase III metastatic breast cancer trial, the toxicity of single agent nab-paclitaxel (260 mg/m^2 every 3 weeks) was compared with that mediated by CrEL-paclitaxel (175 mg/m^2 every 3 weeks) (Gradishar et al, 2005) (Table 1). Treatment compliance of both groups was equally high with 96% (nab-paclitaxel) or 94% (CrEL-paclitaxel) of patients receiving 90% of the protocol-specified dose despite a higher dose-intensity of paclitaxel in the nab-paclitaxel group (85.1 mg/m^2/week) than the CrEL-paclitaxel group (57.02 mg/m^2/week). Treatment discontinuation, dose reduction and dose delay due to adverse events were also infrequent in both treatment groups. In addition, the safety profile of nab-paclitaxel was comparable to that of CrEL-paclitaxel although there were some differences between the two groups. Consistent with the safety data, no differences in quality of life (QOL) were observed between the two groups.

Table 1.

Frequency of important adverse events: nab-paclitaxel 260 mg/m^2 versus CrEL-paclitaxel 175 mg/m^2

Adverse events	Nab-paclitaxel (n = 229)		CrEL-paclitaxel (n = 225)	
	All grade	≥Grade 3	All grade	≥Grade 3
Hematologic				
Neutropenia	80%	34%	82%	53%
Thrombocytopenia	12%	<1%	15%	<1%
Anemia	47%	1%	43%	<1%
Febrile neutropenia	2%	2%	1%	1%
Infection	15%	4%	14%	2%
Nonhematologic				
Hypersensitivity reaction	4%	0%	12%	2%

Grade 4 neutropenia was significantly lower in the nabpaclitaxel group than in the CrEL-paclitaxel group (9% vs 22%, respectively; $P < 0.0001$). These findings suggest that the CrEL vehicle may be responsible for the noted toxicity in patients treated with CrEL-paclitaxel. Hematologic toxicities were dose-dependent and reversible.

Hypersensitivity reactions, such as dyspnea, flushing, chest pain, hypotension, and arrhythmia, can occur during infusion of drugs. Almost all patients treated with nabpaclitaxel received no premedication. On the other hand, almost all patients treated with CrEL-paclitaxel received premedication with corticosteroids and antihistamines to avoid hypersensitivity reaction. The incidence of this adverse event was low for both groups in the randomized trial. The incidence of severe hypersensitivity reaction was 2% in the CrEL-paclitaxel group despite their having received standard premedication.

As expected, with a higher dose of paclitaxel, the incidence of a severe sensory neuropathy was greater in the nab-paclitaxel group than the CrEL- paclitaxel group (10% vs 2%, respectively; $P < 0.001$), as well as the overall incidence of this toxicity (71% vs 56%, respectively; $P < 0.05$), in the pivotal randomized comparative study. Nabpaclitaxel- induced peripheral neuropathy could be managed with treatment interruption and dose reduction.

1.8. Rationale for the Study

Pancreatic cancer is responsible for 38,000 deaths per year, and is the fourth most common cause of death from cancer in both sexes combined, a position relatively high when compared to incidence (tenth position) because of the very poor prognosis (the M/I ratio is 98%) (Siegel R et al, 2013). The incidence of pancreatic carcinoma has increased almost 300% since 1950 and now exceeds the incidence of stomach cancer. Carcinoma of the exocrine pancreas is nearly always a fatal disease. The overall 5-year survival rate for the disease is approximately 4%.

Locally advanced or metastatic pancreatic cancer is relatively unresponsive to chemotherapy. Gemcitabine therapy provides some benefit and modestly improves survival compared with fluorouracil, but median survival in patients with advanced disease remains less than 6 months (Burris HA et al, 1997). Cytotoxic drug combinations were not able to show survival advantage compared to Gemcitabine alone in numerous randomized phase III studies.

Nab-paclitaxel is an albumin-bound nanoparticle form of paclitaxel. Nab-paclitaxel demonstrated the capacity of increasing the gemcitabine bioavailability inside the tumors in a preclinical study (Von Hoff et al, 2011). This was followed by a phase I/II study demonstrating feasibility of nab-paclitaxel in combination with gemcitabine in metastatic pancreatic cancer.

Following this initial study, phase III MPACT study (Metastatic Pancreatic Adenocarcinoma Clinical Trial) including 861 patients showed statistically significant and clinically meaningful improvements in all endpoints across all subgroups compared with gemcitabine alone including overall survival. This combination may represent a new standard in the management of these patients and could become a "backbone" in future trials in these patients.

The effect of Nab-paclitaxel plus gemcitabine combination on QoL of patients with metastatic pancreatic cancer has not been analyzed. The objective of the trial is to compare QoL in patients receiving Nab-Paclitaxel plus Gemcitabine versus gemcitabine. QoL will be assessed using the EORTC QLQ-C30 for at least 12 months (in those who are still alive) for all patients (even if they deteriorate 10 points and meet the study end point).

2. STUDY OBJECTIVES

2.1. Primary study objectives

- **3-months deterioration-free rate (percentage of patients free from definitive deterioration).** EORTC QLQ-C30 (validated version for Turkish using a reduction of at least 10 points as a meaningful clinical difference) will be used to calculate "time until definitive deterioration" (TUDD) and compare patients receiving first-line Nab-Paclitaxel plus Gemcitabine versus first-line gemcitabine for metastatic or locally advanced unresectable adenocarcinoma of the pancreas. EORTC QLQ-C30 scores will be calculated every four weeks following the EORTC QLQ-C30 recommendations for calculations and scoring (EORTC QLQ-C30 published manual).

2.2. Secondary study objectives

- Overall survival (OS).

- Progression-free survival (PFS).
- Response rate.
- Safety and toxicity
- Predictive and prognostic factors: Serum and archived tumor tissue biomarkers (available patients) for prognosis and prediction to response to treatment and toxicity.

3. INVESTIGATIONAL PLAN

3.1. Study Design

Arm 1:

Nab-paclitaxel 125 mg/m2 as 30- to 40-minute infusion (maximum infusion time not to exceed 40 minutes) once weekly for 3 weeks followed by a week of rest.

plus

Gemcitabine 1000 mg/m2 as a 30- to 40-minute infusion (maximum 40 minutes) once weekly for 3 weeks followed by a week of rest.

OR

Arm 2:

Gemcitabine 1000 mg/m2 as a 30- to 40-minute infusion (maximum 40 minutes) administered weekly for 7 weeks followed by a week of rest (8-week cycle; cycle 1 only), followed by cycles of weekly administration for 3 weeks (on days 1, 8, and 15) followed by one week of rest (4-week cycle).

All patients will be considered for available second-line therapies or best supportive care on the discretion of the investigators.

3.2. Study Duration

The first patient is planned to be enrolled in March 2014. The recruitment period is estimated to be around 14 months.

Patients will receive study treatment until death, disease progression (PD), occurrence of intolerable side effects, or withdrawal of consent, whichever comes first.

All patients will be followed for QoL and survival.

A patient is considered “Discontinued from Study Follow-up” only if study treatment has been discontinued **AND** one of the following occurs:

a. Patient withdraws consent.

b. Patient is lost to follow-up.

c. Patient dies.

d. Patient completes 1-year follow-up.

e. Study is completed or terminated by the Sponsor.

3.3. Study Population

Chemotherapy-naïve patients presenting with metastatic or unresectable locally advanced pancreatic adenocarcinoma and a measurable disease by RECIST.

3.4. Inclusion Criteria

A patient must meet all of the following inclusion criteria to be eligible for enrollment in this study:

1. Written informed consent.
2. Histologically or cytologically confirmed treatment-naïve metastatic or locally advanced adenocarcinoma of the pancreas not amenable to curative radiotherapy or surgery.
3. Measurable disease as defined by RECIST (ie, target lesions that can be accurately measured in at least one dimension with the longest diameter ≥ 20 mm using conventional techniques or ≥ 10 mm using spiral computed tomography [CT] scan).
4. Age ≥ 18 years.
5. ECOG Performance Status 0 or 1.
6. Adequate bone marrow function: granulocyte count ≥1500 and platelet count ≥100,000 per cubic milimeter.
7. Adequate liver function as defined by the following criteria:
   - Total serum bilirubin <2 mg/dl.
   - ALP/GGT <5 x ULN.

- Transaminases ALT/AST ≤ 2.5 x ULN.

3.5. Exclusion Criteria

1. Any prior systemic or investigational therapy for metastatic pancreatic cancer. Systemic therapy administered alone or in combination with radiation in the adjuvant setting is permitted if it is completed > 6 months prior to the time of study enrollment.
2. Inability to comply with study and/or follow-up procedures.
3. Presence of significant comorbidity including clinically significant cardiac disease (e.g. congestive heart failure, symptomatic coronary artery disease and cardiac arrhythmias not well controlled with medication) or myocardial infarction within the last 12 months and any other major organ failure.
4. Presence of any condition that, in the opinion of the investigator, renders the subject at high risk from treatment complications or might affect the interpretation of the results of the study.
5. Presence of central nervous system or brain metastases.
6. Life expectancy <12 weeks.
7. Pregnancy (positive pregnancy test) or lactation.
8. Prior malignancy except for adequately treated basal cell skin cancer, in situ cervical cancer, adequately treated Stage I or II cancer from which the patient is currently in complete remission, or any other form of cancer from which the patient has been disease-free for 5 years.
9. Lack of physical integrity of the upper gastrointestinal tract or malabsorption syndrome.
10. Known, existing uncontrolled coagulopathy.
11. Pre-existing sensory neuropathy > grade 1.
12. Major surgery within 4 weeks of the start of study treatment, without complete recovery.

13. Concurrent/pre-existing use of coumadin.

14. Patients older than 76 years of age.

15. Patients with active infection.

16. Patients with chronic diarrhea.

4.0 STUDY MEDICATION

4.1. Provision of the study medication

NAB-PACLITAXEL

Nab-paclitaxel is available as lyophilized powder in vials containing 100 mg paclitaxel individually packaged in a cartonEach vial is reconstituted by injecting 20 mL of 0.9% Sodium Chloride Injection.

Each mL of the reconstituted formulation will contain 5 mg/mL paclitaxel. Inject the appropriate amount of reconstituted drug into an empty, sterile intravenous bag [plasticized polyvinyl chloride (PVC) containers, PVC or non-PVC type intravenous bag]. The use of specialized DEHP-free solution containers or administration sets is not necessary to prepare or administer nab-paclitaxel infusions. The use of an in-line filter is not recommended.

GEMCITABINE

Gemcitabine is available as lyophilized powder in vials of 200 mg and 1000 mg. The powder is constituted with 5 mL and 25 mL of sodium chloride 0.9% iv infusion solution, respectively. The solution may be further diluted with sodium chloride 0.9% infusion solution.

4.2. Stability/Application

Unopened vials of ABRAXANE are stable until the date indicated on the package when stored between 20ºC to 25ºC (68ºF to 77ºF) in the original package. Neither freezing nor refrigeration adversely affects the stability of the product.

Stability of Reconstituted Suspension in the Vial

Reconstituted ABRAXANE in the vial should be used immediately, but may be refrigerated at 2ºC to 8ºC (36ºF to 46ºF) for a maximum of 8 hours if necessary. If not

used immediately, each vial of reconstituted suspension should be replaced in the original carton to protect it from bright light. Discard any unused portion.

Stability of Reconstituted Suspension in the Infusion Bag

The suspension for infusion when prepared as recommended in an infusion bag should be used immediately but may be stored at ambient temperature (approximately 25ºC) and lighting conditions for up to 4 hours. Discard any unused portion.

4.3. Storage

The vials should be stored in original cartons at 20ºC to 25ºC and in the original package to protect from bright light. All study medication must be kept in a locked area with restricted access to specific study personnel.

4.4. Accountability

In accordance with International Conference on Harmonisation (ICH) and United States Food and Drug Administration (FDA) requirements, the Investigator and/or pharmacist must at all times be able to account for all study agents furnished to the institution. The appropriate site personnel must acknowledge receipt of all study medication by signing, dating and immediately faxing the medication packing form included with each shipment.

Record the use of the study medication on the appropriate Drug Accountability Record (DAR). All study medication must be accounted for, whether used or unused, by the Investigator and/or pharmacist during the course of and at the conclusion of the study. The Study Monitor will check the supplies of study medication and will review the accountability records during monitoring visits. Study medication reconciliation will be completed at the end of the study.

At the conclusion of the study or early termination of patients, all used and unused study medication of that patient shipped to the Investigator must be returned to the designated sponsor accompanied by a study medication reconciliation form (unless site policy requires on-site destruction). If on-site destruction is policy, such requirement must be documented in the institution’s Standard Operating Procedure (SOP) and provided to the designated sponsor for review. No study medication is to be used outside of this study.

4.5. Study concomitant treatments, medication administration and dose modification procedures

4.5.1. Concomitant treatments

Hematologic Support

Hematologic support (including prophylactic use) as medically indicated is permitted (eg, blood transfusions, granulocyte-colony stimulating factor [G-CSF], etc) according to the institutional site standards. (If there are no standard procedures for the use of growth factors, follow American Society of Clinical Oncology [ASCO] Guidelines for Use of Hematopoietic Colony-Stimulating Factors available at www.asco.org).

Other Supportive Treatment

Supportive treatments such as antiemetics, analgesics, etc, are permitted and should be administered according to the institutional standard of care. Analgesic consumption will be monitored and recorded throughout the study.

A mouth rinse is permitted as a curative or prophylactic treatment for stomatitis.

Palliative Radiotherapy

Concurrent radiotherapy is not permitted. If palliative radiotherapy is required the patient will be off study. Thorough clinical examination for presence of PD is then recommended.

All concomitant treatments will be recorded in the CRF.

4.5.2. Treatment

Arm 1:

Nab-paclitaxel 125 mg/m2 as 30- to 40-minute infusion (maximum infusion time not to exceed 40 minutes) once weekly for 3 weeks followed by a week of rest.

plus

Gemcitabine 1000 mg/m2 as a 30- to 40-minute infusion (maximum 40 minutes) once weekly for 3 weeks followed by a week of rest.

OR

Arm 2:

Gemcitabine 1000 mg/m2 as a 30- to 40-minute infusion (maximum 40 minutes) administered weekly for 7 weeks followed by a week of rest (8-week cycle; cycle 1 only), followed by cycles of weekly administration for 3 weeks (on days 1, 8, and 15) followed by one week of rest (4-week cycle).

BSA will be calculated according to site standard practice. If no standard is available, the DuBois formula provided below should be used. BSA should be calculated to two decimal places:

$$BSA\ (m^2) = ([Weight\ (kg)]^{0.425}) \times ([Height\ (cm)]^{0.725}) \times 0.007184$$

If the patient's weight increases or decreases by ≥ 10% from the previous calculation (e.g. start of previous treatment cycle), and is clearly not related to fluid retention, the patient's BSA must be recalculated at the start of a new cycle.

4.5.3. Dose delays and modifications

Rules for Dose Omissions and Modified Schedules

Day 1 dose missed;

If the dose held or missed was to be given on Day 1 of the next cycle, that next cycle will not be considered to start until the day the first dose is actually administered to the patient (ie, 1-2-3-Rest, X-1-2-3-Rest, etc).

Day 8 dose is missed;

Cycle continues per protocol, with one dose not given (ie, 1-2-3-Rest, 1-X-3-Rest, 1-2-3-Rest, etc). Day 15 is administered as per cycle calendar if counts and chemistries permit.

Day 15 dose missed;

That week becomes the week of rest. Next dose (if counts and chemistries permit) becomes Day 1 of a new cycle, and the patient is considered to have had a x2q3 (21-day) cycle (ie, 1-2-3-Rest, 1-2-X, 1-2-3-Rest, etc).

The maximum delay: The maximum delay between a missed scheduled dose and the next one (whichever dose was missed) should not be longer than 21 days (except for peripheral neuropathy)

Two dose modifications are permitted. If a toxicity requiring dose modification occurs following the second dose reduction of either drug, further treatment should be discontinued.

Table 2: Dose Modifications

Dose Level	**NAB-PACLITAXEL Dose (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 Tables 2-4 for specific recommendations regarding dose reductions.

b) A maximum of 2 dose-level reductions are allowed.

Patients experiencing study drug-related toxicities that require a delay in scheduled NAB-PACLITAXEL or gemcitabine dosing for ≥21 days will be discontinued from further treatment in this study (except for peripheral neuropathy). When a dose reduction is required, no dose re-escalation will be permitted for the duration of study treatment.

DOSE MODIFICATIONS AT DAY 1;
In the event dose modifications are required at the beginning of a cycle due to AEs or hematologic toxicities, doses of NAB-PACLITAXEL and gemcitabine may be adjusted

Table 3: Dose modifications for Day 1 of each cycle (hematologic toxicity);

Treatment day counts and toxicity			
ANC	**Platelets**		**Timing**
≥1.5 x 109/L	And	≥100 x 109/L	Treat on time
<1.5 x 109/L	Or	<100 x 109/L	Delay by 1 week intervals until recovery

Table 4: Dose modifications for Day 1 of each cycle (non-hematologic toxicity)

Non-Hematologic Toxicity and/or Dose Hold with Previous Cycle	
Toxicity/dose held	**Gemcitabine/Gemcitabine+nab-paclitaxel dose this cycle**
Grade 0, 1 or 2 toxicity	Same as Day 1 previous cycle (except for cutaneous toxicity)
Grade 3 toxicity	Decrease gemcitabine and nab-paclitaxel to next lower dose level
Grade 4 toxicity	Off protocol treatment
Dose held in 2 previous consecutive cycles	Decrease gemcitabine to next lower dose level and continue throughout the rest of treatment

a) If the toxicity only affects neuropathy, then only nab-paclitaxel should be reduced

b) Pulmonary embolism (Grade 4 toxicity in the CTCAE tables) if mild or asymptomatic, will be exempt from this requirement.

Gemcitabine and nab-paclitaxel or gemcitabine monotherapy will be provided within the study protocol until patients progress or are unable to tolerate the treatment.

Patients on single-agent gemcitabine arm will be allowed cross-over to the combination arm in case of a definitive deterioration in the GHS score of at least 10 points.

5.0. STUDY SCHEDULE AND PROCEDURES

5.1. Study schedule

THERAPY SYNOPSIS		**NAME, SURNAME** Birthday -- -- ---- STID - - -		
	DAY	**WEEK**	**NABPACLITAXL**	**GEMCITABINE**
CT/ MRI (SCREENING)				**QoL**
APPLICATION WEEKLY: Nab-paclitaxel 125 mg/m2 Plus Gem 1000 mg/m2 (3 weeks on, 1 week off) **OR** Gem 1000 mg/m2 iv 30'	**1**	**1**		
	8	**2**		
	15	**3**		
	22	**4**	**REST**	
	29	**5**		
	36	**6**		**QoL**
	43	**7**		
CT / MRI (FOLLOW UP # 1)	**50-56**	**8**	**PD: OFF STUDY SD/PR/CR: FURTHER THERAPY**	
APPLICATION WEEKLY: Nab-paclitaxel 125 mg/m2 Plus Gem 1000 mg/m2 (3 weeks on, 1 week off) **OR** Gem 1000 mg/m2 iv 30'	**57**	**9**		
	64	**10**		
	71	**11**		
	78	**12**	**REST**	
	85	**13**		
	92	**14**		**QoL**
	99	**15**		
CT / MRI (FOLLOW UP # 2)	**106-112**	**16**	**PD: OFF STUDY SD/PR/CR: FURTHER THERAPY**	
APPLICATION WEEKLY: (see above, CT/ MRI follow up every 7-8 weeks)	**113**	**17**		
	120	**18**		
	127	**19**		
	134	**20**	**REST**	

5.2. Study procedures

5.2.1. Informed consent

Obtain signed and dated ICF from the patient prior to the implementation of any study procedures required by the protocol. Give a signed and dated copy of the completed ICF to the patient.

5.2.2. Medical history and cancer related signs and symptoms

Obtain a complete medical history at Baseline within 7 days prior to planned study medication administration on Day 1 of Week 1. Record the patient's medical history in the Medical History section of the CRF.

Signs and symptoms present within 7 days prior to study medication administration on Day 1of Week 1 should be recorded on the Existing Signs and Symptoms Related to Cancer section of the CRF.

5.2.3. Physical examination

Perform a complete physical examination at the time points listed below:

- Baseline within 7 days prior to study medication administration on Day 1
- At the beginning of every new cycle
- At the end of study treatment

5.2.4. Vital signs, weight, and height

Obtain the patient's height at baseline within 7 days prior to dosing on Day 1.

Collect the patient's vital signs (blood pressure, heart rate, body temperature, and respiratory rate) and weight (also recalculate BSA if weight changes by ≥ 10% from previous calculation; see Section 0) at the time points listed below. Obtain all the vital signs in a position that is consistent for all time points for each patient.

- Baseline within 7 days prior to first study medication administration on Day 1
- Within 24 hours prior to each subsequent study drug medication
- At the end of study treatment

5.2.5. Performance Status and quality-of-life (QoL) assessment

ECOG performance status score will be measured by a qualified person at the site at the following time points:

- Baseline within 7 days prior to first study medication administration on Day 1
- Within 24 hours prior to each subsequent study drug administration
- At the end of study treatment

The same person should obtain PS at baseline and at each assessment throughout the study for a given patient.

Quality-of-Life will be assessed with the EORTC QLQ -C30 module at the following time points:

- Baseline within 7 days prior to first study medication administration on Day 1
- Every 4 weeks.
- At the end of study treatment
- The questionnaire will be completed by the patient.

5.2.6. Electrocardiogram (ECG)

Perform a 12-lead ECG at Baseline within 28 days prior to first study medication administration on Day 1.

5.2.7. Chest X-ray (CXR)/Chest Computed Tomography (CT)

Perform a CXR at Baseline within 14 days prior to first study medication administration as part of Baseline physical examination. If chest CT is obtained as part of the baseline tumor assessment, the chest X-ray can be omitted.

5.2.8. Clinical Laboratory Evaluations

5.2.8.1. Hematology

Collect blood for hematology assessments at the following time points and when clinically indicated:

- Baseline within 7 days prior to first administration of study medication on Day 1
- Prior to each subsequent study drug medication
- At the end of study treatment

Measure the following hematology parameters (before each application):

Table 5: Hematology parameters measured before each application

Red Blood Cell (RBC) count
Hemoglobin
Hematocrit
Platelets
White Blood Cell (WBC)

Measure the following hematology parameters (before start of new cycle):

Table 6: Hematology parameters measured before start of new cycle

Red Blood Cell (RBC) count	White Blood Cell (WBC) count with differential
Hemoglobin	Neutrophils
Hematocrit	Lymphocytes
Platelets	Basophils
Quick	Monocytes
Thrombin time	Eosinophils
Partial thrombin time	

5.2.8.2. Serum Chemistry

Collect blood for serum chemistry assessments at the following time points:

- Baseline within 7 days prior to study medication administration on Day 1
- Within 24 hours prior to study drug medication on Days 1 of every new cycle all parameters (see below) plus tumor marker.
- At the end of study treatment

Table 7: Serum chemistry measurements

Total protein	Calcium
Alkaline phosphatase	Creatinine[a]
Alanine aminotransferase (ALT; SGPT)	Lactic dehydrogenase (LDH)
Aspartate aminotransferase(AST; SGOT)	Blood Glucose
Bilirubin	Potassium
Gamma-GT	Magnesium
Blood Urea Nitrogen (BUN)	Sodium
CA 19-9	
[a] Calculated creatinine clearance (CrCl) should be calculated before each subsequent cycle of treatment according to Cockcroft-Gault formula.	

5.2.8.3.Urinalysis

Collect urine samples at the time points listed below:

- Baseline within 7 days prior to study medication administration on Day 1
- At the end of study treatment

Measure protein, glucose, RBC and WBC semiquantitatively by dipstick.

5.2.9. Pregnancy test

If the patient is female and of child-bearing potential, exclude the possibility of pregnancy by testing serum or urine Beta Human Chorionic Gonadotrophin (β-HCG) within 7 days prior to the start of study medication administration on Day 1. For urine β-HCG pregnancy test, record the date, time and test results in the patient's source documents.

Female patients who are not of child-bearing potential must have a history of being post-menopausal with a minimum of 1 year without menses, tubal ligation or hysterectomy.

5.2.10. Carbohydrate antigen (CA) 19-9 levels

Blood samples for analysis of serum CA19-9 levels will be obtained at the following timepoints:

- Baseline within 7 days prior to study medication administration on Day 1

- At the beginning of every new cycle
- At the end of study treatment

5.2.11. Concomitant medications and therapies

Record all medications, prescription and over-the-counter, in the Concomitant Medication section of the CRF. Additionally, record modifications to these medications and newly prescribed pharmacological treatments and therapeutic measures in this section. Analgesic consumption will be monitored and recorded throughout the study as a component of the QoL-assessment (5.2.5).

Collect concomitant medication information from time of signed ICF through the end of treatment. Any concomitant medication used to treat AEs during the 30 days after administration of last dose of study medication should also be collected. Otherwise, collect only anti-cancer therapy during follow-up. Use of concomitant medication should be documented in the patient's source documents.

5.2.12. Adverse event and toxicity assessment

Monitor patients for any untoward medical events from the time of signed ICF through end of treatment, including any AEs and SAEs reported during the 30-day follow-up period.

5.2.13. Tumor assessments/scans

Tumor assessments/scans must be obtained at the time points listed below for all patients; however, if a patient develops PD, discontinue treatment with study medication. The same method of assessment and the same technique must be used to characterize each identified and reported lesion at Baseline, throughout the study.

Table 8: Tumor assessments.

Baseline	During week 8, 16, 24, etc)[a]
Within 2 weeks prior to Day 1	Within 7 days prior to initiation of subsequent cycle
[a] If a patient discontinues for reason other than PD, obtain imaging studies for tumor assessment prior to initiation to another treatment regimen.	

On-site tumor assessments will be performed by the Investigator/local radiologist. Results of these assessments will be the basis for the continuation or discontinuation of treatment. Tumor scans must be collected and forwarded for independent review.

For a patient who responds, response confirmation would be obtained earliest 4 and preferably 6 weeks after the first documentation of response.

The same schedule for clinical assessments should be followed. If the patient develops PD during clinic visits, study treatment should be discontinued.

All radiological images must be available for source verification. Images will be submitted for extramural review for final assessment of antitumor activity.

5.2.13.1. Tumor measurements

The determination of antitumor efficacy will be based on objective tumor assessments. Tumor assessments will be based on the RECIST criteria of unidimensional evaluation as determined by a Core Imaging Laboratory.

5.2.13.2. Methods of measurement

The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during follow-up. Imaging-based evaluation is preferred to evaluation by clinical examination when both methods have been used to assess the antitumor effect of treatment. All measurements should be recorded in metric notation using a ruler or calipers.

Contrast enhanced CT is the preferred method for tumor assessments. If contrast CT is contraindicated in a patient, then magnetic resonance imaging (MRI) should be used. Conventional CT and MRI should be performed with cuts of 10 mm or less in slice thickness contiguously. Spiral CT should be performed using a 5 mm or less contiguous reconstruction algorithm. This applies to the chest, abdomen, and pelvis. Clinical lesions will only be considered measurable when they are superficial (eg, skin nodules, palpable lymph nodes). In the case of skin lesions, documentation by color photography including a ruler to estimate the size of the lesion is recommended.

Ultrasound (US) should not be used to measure tumor lesions that are clinically not easily accessible for objective response evaluation (eg, visceral lesions). Ultrasound is a possible alternative to clinical measurements of superficial palpable nodes, subcutaneous lesions, and thyroid nodules. Ultrasound might also be useful to confirm

the complete disappearance of superficial lesions usually assessed by clinical examination.

5.2.13.3. Measurability of lesions

At baseline, lesions will be categorized by the Investigator as measurable or non-measurable and as target and non-target lesions by the RECIST as described below.

- Measurable: Lesions that can be accurately measured in at least one dimension with the longest diameter (to be recorded) ≥ 20 mm with conventional techniques or ≥ 10 mm with spiral CT scan.
- Non-Measurable: All other lesions, including small lesions (longest diameter < 20 mm with conventional techniques or < 10 mm with spiral CT scan), ie, bone lesions, leptomeningeal disease, ascites, pleural/pericardial effusion, inflammatory breast disease, lymphangitis cutis/pulmonis, cystic lesions, and abdominal masses that are not confirmed and followed by imaging techniques.

Recording Tumor Measurements

All measurable and non-measurable lesions should be identified at baseline and at the stipulated intervals during treatment.

One or two lesions will be defined as target lesions. The target lesions should be selected on the basis of its size (lesions with the longest and second-longest diameter) and its suitability for accurate measurements by imaging techniques. The diameters will be recorded for the target lesions. The sum of the longest diameters as determined at baseline will be used as a reference to further characterize the objective tumor response during treatment.

All measurements should be performed using a caliper or ruler and should be recorded in metric notation in centimeters.

All other lesions (or sites of disease) should be identified as non-target lesions and should also be recorded at baseline. Measurements are not required, and these lesions should be followed as “present” or “absent.”

Tumor response assessment

Only measurable lesions will be assessed for tumor response.

Table 9: Tumor response assessment of target lesions.

Target Lesions Response:	**Definition:**
Complete Response (CR)	The disappearance of all target lesions
Partial Response (PR)	At least a 30% decrease in the sum of the longest dimensions of target lesions, taking as a reference the baseline sum of longest dimensions
Progressive Disease (PD)	At least a 20% increase in the sum of the longest dimensions of the target lesions, taking as a reference the smallest sum of the longest dimensions recorded since the treatment started, or the appearance of one or more new lesions
Stable Disease (SD)	Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD taking as a reference the smallest sum of the longest dimensions since the treatment started
[a] Modified from RECIST criteria	

Table 10: Tumor response assessment of non-target lesions.

Non-Target Lesions Response:	**Definition:**
Complete Response (CR)	The disappearance of all non-target lesions and normalization of tumor marker level
Incomplete Response (non-CR)/ Stable disease (SD)	A persistence of $\geq$ 1 non-target lesion(s) and/or maintenance of tumor marker level above the normal limits
Progressive Disease (PD)	Appearance of one or more new lesions and/or unequivocal progression of existing non-target lesions
[a] Modified from RECIST criteria	

The cytological confirmation of the neoplastic origin of any effusion that appears or worsens during treatment when the measurable tumor has met criteria for response or SD is mandatory to differentiate between response and SD or PD.

The overall assessment of response will involve all parameters as depicted below. The best overall response is the best response recorded from the start of the treatment until disease progression/recurrence (taking as reference for tumor progression the smallest

measurements recorded since the treatment started), until 30 days after end of individual treatment, death or lost to follow up.

Table 11: Overall assessment of response.

Target Lesions	Non-target Lesions	New Lesions	Overall Response
CR	CR	No	CR
CR	Incomplete Response/Stable Disease (SD)	No	PR
PR	Non-PD	No	PR
SD	Non-PD	No	SD
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD

Patients with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be reported as “symptomatic deterioration". Every effort should be made to document the objective progression even after discontinuation of treatment. It should also be noted that a tumor marker increase does not constitute adequate objective evidence of tumor progression. However, such a tumor marker increase should prompt a repeat radiographic evaluation to document whether or not tumor objective tumor progression has occurred.

In some circumstances, it may be difficult to distinguish residual disease from normal tissue. When the evaluation of a CR depends upon this determination, it is recommended that the residual lesion be investigated by fine needle aspirate or biopsy before confirming the CR status.

Confirmation of Tumor Response

To be assigned a status of PR or CR, changes in tumor measurements in patients with responding tumors must be confirmed by repeat studies that should be performed earliest 4 and preferably 6 weeks after the criteria for response are first met. In the case

of SD, measurements must have met the SD criteria at least once after study entry at a minimum interval of 6 weeks.

5.2.14. End of treatment procedures

The end of treatment is defined as the time of withdrawal of study medication (see Discontinuation Criteria). End of treatment assessments will be performed at the time of withdrawal of study medication if a patient discontinued due to toxicity or withdrawn consent. If a patient discontinues treatment due to PD, end of treatment assessments may be collected within 2 weeks of PD assessment.

First-line standard therapy in advanced pancreatic cancer is gemcitabine therapy. There is no established second-line therapy for recurrence patients. Patients in good general condition can be offered therapy with other agents. Provided that appropriate studies are conducted, they can be included in Phase I / II studies with novel agents or new combinations.

5.2.15. Follow-up study procedures

If a patient discontinues treatment for any reason prior to 1 year from first day of treatment, survival status will be collected every 2 months. For the same time period, also record any other antitumor therapies received.

Following premature discontinuation of study treatment for reasons other than withdrawal of consent, death, or PD, follow all patients for tumor response every 6 weeks until PD or initiation of non-study anti-cancer therapy. The same collection and documentation procedures conducted during the treatment period apply to the follow-up period.

6.0. REPORTING SAFETY INFORMATION

6.1. Monitoring, Recording and Reporting of Adverse Events

An adverse event (AE) is any noxious, unintended, or untoward medical occurrence that may appear or worsen in a subject during the course of a study. It may be a new intercurrent illness, a worsening concomitant illness, an injury, or any concomitant impairment of the subject’s health, including laboratory test values (as specified by the criteria below), regardless of etiology. Any worsening (i.e., any clinically significant adverse change in the frequency or intensity of a pre-existing condition) should be

considered an AE. A diagnosis or syndrome should be recorded on the AE page of the CRF rather than the individual signs or symptoms of the diagnosis or syndrome.

Disease progression is not to be reported as an adverse event. Pancreatic cancer is expected to progress under treatment; therefore progression can not be regarded as AE (See 2.Study Objectives and 7.2. Secondary aims and secondary endpoints).

An overdose, accidental or intentional, whether or not it is associated with an AE, or abuse, withdrawal, sensitivity or toxicity to an investigational product should be reported as an AE. If an overdose is associated with an AE, the overdose and adverse event should be reported as separate terms.

All subjects will be monitored for AEs during the study. Assessments may include monitoring of any or all of the following parameters: the subject's clinical symptoms, laboratory, pathological, radiological or surgical findings, physical examination findings, or other appropriate tests and procedures.

All AEs will be recorded by the Investigator from the time the subject signs informed consent to 30 days after the last dose of IP or until the last study visit, whichever period is longer. AEs and serious adverse events (SAEs) will be recorded on the AE page of the CRF and in the subject's source documents. All SAEs must be reported to sponsor within 24 hours of the Investigator's knowledge of the event by facsimile, or other appropriate method, using the SAE Report Form, or approved equivalent form.

6.2. Evaluation of Adverse Events

A qualified Investigator will evaluate all adverse events as to:

6.2.1. Seriousness

A serious adverse event (SAE) is any AE occurring at any dose that:

- Results in death;
- Is life-threatening (i.e., in the opinion of the Investigator, the subject is at immediate risk of death from the AE);
- Requires inpatient hospitalization or prolongation of existing hospitalization (hospitalization is defined as an inpatient admission, regardless of length of stay);

- Results in persistent or significant disability/incapacity (a substantial disruption of the subject's ability to conduct normal life functions);
- Is a congenital anomaly/birth defect;
- Constitutes an important medical event.

Important medical events are defined as those occurrences that may not be immediately life threatening or result in death, hospitalization, or disability, but may jeopardize the subject or require medical or surgical intervention to prevent one of the other outcomes listed above. Medical and scientific judgment should be exercised in deciding whether such an AE should be considered serious.

Events **not considered** to be SAEs are hospitalizations for:

- A standard procedure for protocol therapy administration. However, hospitalization or prolonged hospitalization for a complication of therapy administration will be reported as an SAE.
- Routine treatment or monitoring of the studied indication not associated with any deterioration in condition.
- A procedure for protocol/disease-related investigations (e.g., surgery, scans, endoscopy, sampling for laboratory tests, bone marrow sampling). However, hospitalization or prolonged hospitalization for a complication of such procedures remains a reportable SAE.
- Hospitalization or prolongation of hospitalization for technical, practical, or social reasons, in absence of an AE.
- A procedure that is planned (i.e., planned prior to starting of treatment on study); must be documented in the source document and the CRF. Hospitalization or prolonged hospitalization for a complication remains a reportable SAE.
- An elective treatment of a pre-existing condition unrelated to the studied indication.
- Emergency outpatient treatment or observation that does not result in admission, unless fulfilling other seriousness criteria above.

If an AE is considered serious, both the AE page/screen of the CRF and the SAE Report Form must be completed.

For each SAE, the Investigator will provide information on severity, start and stop dates, relationship to IP, action taken regarding IP, and outcome.

6.2.2. Severity / Intensity

For both AEs and SAEs, the Investigator must assess the severity / intensity of the event.

The severity / intensity of AEs will be graded based upon the subject's symptoms according to the current active minor version of National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE, Version 4.0); http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm#ctc_40

AEs that are not defined in the NCI CTCAE should be evaluated for severity / intensity according to the following scale:

- *Grade 1 = Mild – transient or mild discomfort; no limitation in activity; no medical intervention/therapy required*
- *Grade 2 = Moderate – mild to moderate limitation in activity, some assistance may be needed; no or minimal medical intervention/therapy required*
- *Grade 3 = Severe – marked limitation in activity, some assistance usually required; medical intervention/therapy required, hospitalization is possible*
- *Grade 4 = Life threatening – extreme limitation in activity, significant assistance required; significant medical intervention/therapy required, hospitalization or hospice care probable*
- *Grade 5 = Death - the event results in death]*

The term "severe" is often used to describe the intensity of a specific event (as in mild, moderate or severe myocardial infarction); the event itself, however, may be of relatively minor medical significance (such as severe headache). This criterion is *not* the same as "serious" which is based on subject/event *outcome* or *action* criteria associated with events that pose a threat to a subject's life or functioning.

Seriousness, not severity, serves as a guide for defining regulatory obligations.

6.2.3. Causality

The Investigator must determine the relationship between the administration of IP and the occurrence of an AE/SAE as Not Suspected or Suspected as defined below:

Not suspected: The temporal relationship of the adverse event to IP administration makes **a causal relationship unlikely or remote**, or other medications, therapeutic interventions, or underlying conditions provide a sufficient explanation for the observed event.

Suspected: The temporal relationship of the adverse event to IP administration makes **a causal relationship possible**, and other medications, therapeutic interventions, or underlying conditions do not provide a sufficient explanation for the observed event.

6.2.4. Duration

For both AEs and SAEs, the Investigator will provide a record of the start and stop dates of the event.

6.2.5. Action Taken

The Investigator will report the action taken with IP as a result of an AE or SAE, as applicable (e.g., discontinuation or reduction of IP, as appropriate) and report if concomitant and/or additional treatments were given for the event.

6.2.6. Outcome

The investigator will report the outcome of the event for both AEs and SAEs.

All SAEs that have not resolved upon discontinuation of the subject's participation in the study must be followed until recovered, recovered with sequelae, not recovered (death due to another cause) or death (due to the SAE).

6.3. Abnormal Laboratory Values

An abnormal laboratory value is considered to be an AE if the abnormality:

- results in discontinuation from the study;

- requires treatment, modification/ interruption of IP dose, or any other therapeutic intervention; or
- is judged to be of significant clinical importance.

Regardless of severity grade, only laboratory abnormalities that fulfill a seriousness criterion need to be documented as a serious adverse event.

If a laboratory abnormality is one component of a diagnosis or syndrome, then only the diagnosis or syndrome should be recorded on the AE page/screen of the CRF. If the abnormality was not a part of a diagnosis or syndrome, then the laboratory abnormality should be recorded as the AE.

6.4. Expedited Reporting of Adverse Events

6.4.1. Reporting to Regulatory Authorities and the Ethics Committee

The Sponsor will inform relevant Regulatory Authorities and Ethics Committees;

- Of all relevant information about serious unexpected adverse events suspected to be related to the IP that are fatal or life-threatening as soon as possible, and in any case no later than seven days after knowledge of such a case. Relevant follow-up information for these cases will be subsequently be submitted within an additional eight days
- Of all other serious unexpected events suspected to be related to the IP as soon as possible, but within a maximum of fifteen days of first knowledge by the investigator.

6.4.2. Immediate reporting by Investigator to Sponsor and Sponsor to Celgene

The investigator will inform the Sponsor of all SAEs within 24 hours in order that the sponsor can fulfill their regulatory reporting obligations within the required timeframes.

The Sponsor will supply Celgene with a copy of all SAEs which involve *exposure* to a Celgene product within 24 hours of being made aware of the event regardless of whether or not the event is listed in the reference document (e.g. IB, SmPC).

The contact details of Celgene's Drug Safety Department for the purposes above are:

Celgene Drug Safety Department
Phone: +90 216 600 1108
Fax: +90 216 290 7894
Email: drugsafetyturkey@celgene.com

When necessary, the Investigator/Sponsor may contact the following address for questions regarding the safety of any Celgene product relevant to the Study.

The Sponsor will provide Celgene with a copy of the annual periodic safety report e.g. Development Update Safety Report (DSUR) at the time of submission to the Regulatory Authority and Ethics Committee.

Contact details for Sponsor

Prof. Suayib Yalcin
Hacattepe University Institute of Oncology
Department of Medical Oncology
Sihhiye, Ankara, Turkey
Phone:+90 312 305 2929
Fax: +90 312 305 2905
E-Mail: syalcin@hacettepe.edu.tr

7.0 STATISTICAL ANALYSIS

The biostatistical methods applied for this study are subject to GCP guidelines (Guidelines of the International Conference on Harmonisation [ICH]) e.g.

- ICH E3: Structure and Contents of Clinical Study Reports,

- ICH E6: Good Clinical Practice (GCP). Consolidated Guideline,

- ICH E9: Note for Guidance on Statistical Principles in Clinical Trials.

7.1. Primary aim and primary endpoints

3-months deterioration-free rate (percentage of patients free of definitive deterioration).

Quality of life (QoL): EORTC QLQ-C30 (validated version for Turkish using a reduction of at least 10 points as a meaningful clinical difference) will be used to calculate “time until definitive deterioration” (TUDD) and compare patients receiving first-line Nab-paclitaxel plus gemcitabine versus first-line gemcitabine for metastatic or locally advanced unresectable adenocarcinoma of the pancreas.

7.2. Secondary aims and secondary endpoints

Secondary aims of the trial are the effectiveness of the therapy and characterization of tolerability and safety. The secondary endpoints are analysed in a descriptive way and are not relevant for sample size.

The secondary aims are:

Overall Survival (OS)

Survival is defined as the time from the date of randomization to date of death. In the absence of death confirmation, survival time will be censored at the date of the last study follow up.

Progression-free survival (PFS)

PFS is defined as the time elapsed between treatment initiation and tumor progression or death from any cause, with censoring of patients who are lost to follow-up

Rate of Overall Response (ORR)

ORR is calculated as ratio of the number of patients with confirmed response between 8 and 24 weeks (6 months) over the number of pts evaluable for tumor response within the 8 and 24 weeks after randomization. Responder (CR or PR) are patients in status CR or PR according to RECIST criteria. Confirmation is required earliest after 4 weeks preferably after 6 weeks. Pts without confirmed PR, CR are at best SD.

Safety and toxicity

Predictive and prognostic factors: Serum and archived tumor tissue biomarkers (available patients) for prognosis and prediction to response to treatment and toxicity.

7.3. Safety

Safety will be assessed by the type, incidence, severity (graded by the NCI CTCAE Version 4.0), and relatedness of AEs to treatment and by laboratory assessments.

7.4. Statistical analysis

Sample size calculations will be based on the GHS score considering a 10-point minimal clinically important difference. A definitive deterioration is considered when the score decreases by more than 10 points as compared to baseline. Thus, “time until definitive deterioration” (TUDD) is defined as the time from randomization to the first observation of a definitive deterioration of the score.

The hypotheses for sample size calculations are based on the results of the article “Impact of FOLFIRINOX compared with gemcitabine on quality of life in patients with metastatic pancreatic cancer: results from the PRODIGE/ACCORD 11 randomized trial”, published in Journal of Clinical Oncology.

The curves of TUDD comparing FOLFIRINOX and gemcitabine show that the percentages of patients free from definitive deterioration at 3-months are 83% in the FOLFIRINOX arm and 69% in the gemcitabine arm. Assuming the same for Nab-Paclitaxel plus Gemcitabine arm, these percentages are used as hypotheses for sample size calculations. So, a 3-month deterioration-free rate of 83% for Nab-Paclitaxel plus Gemcitabine arm and 69% for gemcitabine arm will be assumed for calculating the sample size using a log-rank test.

Primary end-point will be 3-months deterioration-free rate (percentage of patients free from definitive deterioration as defined above).

Sample size calculations:

- Hypotheses
    e. 2-sided alpha=0.05
    f. power=80%
    g. accrual 7 pts per month

h. 3-month deterioration-free rate of 83% for Nab-Paclitaxel plus Gemcitabine
i. 3-month deterioration-free rate of 69% for gemcitabine arm

- Results
    a. Accrual duration 14 months
    b. Total study duration 21 months
    c. Total sample size n=100
    d. Number of events E=68 (number of patients with deteriorations).

Accounting for a 20% missing or incomplete forms, the total sample size will be n=125.

8.0 ETHICS

8.1. Ethical considerations

It is mandatory that all considerations regarding the protection of human subjects be carried out in accordance with the protocol, Good Clinical Practices (GCP), ICH, ethical principles that have their origin in the Declaration of Helsinki, and all applicable regulatory requirements.

8.2. Informed consent and patient information

All patients must sign and personally date an approved ICF after receiving detailed written and verbal information about the reason, the nature, and the possible risks associated with the administration of the study medication. This must be done according to the guidelines provided in the Declaration of Helsinki, ICH E6 Guideline for Good Clinical Practice, requirements of Title 21 CFR 50.20 through 50.27.

The patient must be made aware and agree that personal information may be scrutinized during monitoring and audit by competent authorities and properly authorized persons. However, personal information will be treated as strictly confidential and will not be publicly available.

Prior to Institutional Review Board (IRB)/Independent Ethics Committee (IEC) submission, the Investigator must send a copy of the ICF to be used at their institution to the Sponsor/Study Monitor for review to assure compliance with the ICH, local, national, and Code of Federal Regulations (CFR) requirements.

8.3. Institutional review board/independent ethics committee approval

Prior to initiation of the study, the Investigator will submit the study protocol, sample ICF, and any other documents that pertain to patient information, recruitment methods such as patient diaries, and advertisements, to the IRB/IEC. The IRB/IEC must be appropriately constituted, as required in Title 21 CFR 56.107 through 56.115, in Chapter 3 of the ICH E6 Guidelines. The Investigator must also submit any other information that may be requested to the IRB/IEC for review and approval. The Investigator will request that the IRB/IEC provide written approval of the study and will keep on file records of approval of all documents pertaining to this study. A letter confirming the approval must be forwarded to the Study Monitor prior to initiation of this study. This letter will be forwarded to Sponsor prior to the initiation of the study.

The Investigator must submit and, where necessary, obtain approval from the IRB/IEC for all subsequent protocol amendments and changes to the ICF. The Investigator should notify the IRB/IEC of deviations from the protocol or SAEs occurring at the site, as well as other AE reports received from Sponsor, in accordance with local procedures.

The Investigator will be responsible for obtaining annual IRB/IEC approval or renewal throughout the duration of the study. Copies of the Investigator's reports and the IRB/IEC continuance of approval must be sent to the Sponsor.

9.0 ADMINISTRATIVE CONSIDERATIONS

9.1. Regulatory requirements-sponsor/investigator obligations

This study will be conducted in accordance with ICH E6 Guideline, Declaration of Helsinki, local and national requirements, Title 21 CFR 312.50 through 312.70. To ensure compliance the Investigator agrees, by written consent to this protocol, to fully cooperate with compliance checks by allowing access to all documentation by authorized individuals.

9.2. Protocol amendments

No change to the protocol may be made without the joint agreement of both the Investigator and Sponsor. Any amendment to the original protocol will be signed by both parties and submitted to the IRB/IEC and appropriate regulatory authorities for approval or notification.

9.3. Curriculum vitae

The Investigator and any Subinvestigator(s) must provide the Sponsor with current signed and dated (within 1 year) copies of their own curriculum vitae.

9.4. Monitoring procedures

9.4.1. Study monitoring

An initiation visit will be conducted by the Study Monitor to discuss the protocol and the obligations of both the Sponsor and the Investigator. The Investigator must allow the Study Monitor to perform periodic, interim monitoring visits. The purposes of these visits are to:

a. Verify that signed and dated ICF was obtained prior to each patient's participation in the trial.

b. Assess the progress of the study.

c. Review compliance with the study protocol.

d. Determine whether all adverse events were appropriately reported.

e. Determine whether the Investigator is maintaining the essential documents.

f. Discuss any emergent problem.

g. Check the CRF for legibility, accuracy, and completeness.

h. Validate the contents of the CRF against source documents.

i. Assess the status of medication storage, dispensing, and retrieval.

All data required by the protocol must be reported accurately on the CRF and must be consistent with the source documents. Source documents are original documents, data and records (eg, hospital records, clinical and office charts, laboratory notes, memoranda, patients' diaries or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate and complete, microfiches, photographic negatives, microfilm or magnetic media, X-rays or other diagnostic images, patient files, pharmacy records, and laboratory records). The Investigator will make available the source documents for inspection. This information will be considered as confidential.

The Study Monitor will perform a close-out visit at the conclusion of the Investigator's involvement in the study.

9.4.2. Case report form

CRFs must be completed for all patients who sign ICFs even if the patient fails to complete the study. No section of the CRF is to be left blank without an appropriate explanation by the Investigator, since the lack of such explanation may necessitate discarding an otherwise unusable observation.

CRFs must be typed or clearly printed with a black ball point pen; erasable ink, pencil, or free handwriting is not acceptable. Any corrections or deletions are to be made by crossing out with a single line (so it is still legible), then initialing and dating by the Investigator or other authorized person. The use of correction fluids to "white-out" mistakes in data entry is not permitted.

If requested, copies of the CRFs are to be made available to the appropriate regulatory agencies.

9.5. Archiving of records

All unused study materials are to be returned to Sponsor after the study has been completed. The following records must be retained by the Investigator for the maximum period of time as required by the study center. This time period must be at least 2 years after the last approval of the marketing application of the study medication in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or at least 2 years have elapsed since the formal discontinuation of clinical development of the study medication:

a. Protocol.

b. Signed and dated ICF documents for all patients.

c. Patient identification code list, screening log (if applicable), and enrollment log.

d. Record of all communications between the Investigator and the IRB/IEC.

e. Composition of the IRB/IEC or other applicable statement.

f. Record of all communications between the Investigator and Sponsor.

g. List of Sub-investigators and other appropriately qualified persons to whom the Investigator has delegated significant trial-related duties, together with their roles in the study and their signatures.

h. Copies of CRFs and of documentation of corrections for all patients.

i. Drug Accountability Records.

j. Record of any body fluids or tissue samples retained.

k. All other source documents (patient records, hospital records, laboratory records, etc).

l. All other documents as listed in Section 8 of the ICH Consolidated Guideline on GCPs (Essential Documents for the Conduct of a Clinical Trial).

However, because of international regulatory requirements, the Sponsor may request retention for a longer period of time. The Investigator must therefore obtain approval in writing from the Sponsor prior to destruction of any records.

No study document should be destroyed without prior written agreement between Sponsor and the Investigator.

Normally, these records will be held in the Investigator's archives. If the Investigator is unable to meet this obligation, he or she must ask the Sponsor for permission to make alternative arrangements. Details of these arrangements should be documented.

Originals of all documentation and copies of outgoing correspondence concerning the study will be retained in the Trial Master File and stored in a safety area for at least two years after the last approval of a marketing application and until there are no pending or contemplated marketing applications in an ICH region, or for at least 2 years following the formal discontinuation of clinical development of the investigational product, or for a longer period if required by the applicable regulatory requirements. In particular, the final report must be retained by Sponsor or the subsequent owner, for 5 years beyond the lifetime of the study medication.

9.6. Final report

The final report of the trial will be written by the investigator.

9.7. Use and publication of study results

All unpublished documentation (including the protocol, CRF, and IB) given to the Investigator is strictly confidential. All recipients must agree not to disclose the information herein contained to any person without the prior written authorization of Sponsor. The submission of these documents to the IRB/IEC is expressly permitted. The Investigator agrees that Sponsor maintains the right to use the results of this study in their original form and/or in a global report for submission to governmental and regulatory authorities of any country.

The results of the study may be presented during scientific symposia or published in a scientific journal only after review by Sponsor in accordance with the guidelines set forth in the applicable publication or financial agreement.

The Principal Investigator (PI) retains the privilege to be the first presenter of the primary results at a major medical meeting; however, the privilege of presenting data at USA and EU scientific and medical meetings might be offered to the Investigator who accrues the highest number of evaluable patients in the study. All other authors will be in descending order of patient accrual. If the Investigator with the highest accrual chooses not to present the data, the next highest accruing Investigator may take his/her place. In that case, the PI can choose to be the senior author on the abstract(s). The PI will have the privilege to be the first or last author on the primary manuscript originating from this study. The first authorship on secondary publications may be rotated based on accrual. The PI will be senior author on secondary publications (manuscripts/abstracts). The order of all other authors will be based on the number of evaluable patients accrued. It may become necessary for the Sponsor to choose a Writing Committee, if the number of Investigators/potential authors exceeds 12. The Sponsor will be responsible for providing the data to the appropriate Investigators for publication within 12 months of each major analysis, such as the planned interim analyses and final analysis (irrespective of the nature of the results from the study).

9.8. Termination of the study

In the event that the Investigator is unable to continue the study, another suitable person will be designated Investigator, and documentation testifying to this will be submitted to the Study Monitor and Medical Monitor within 10 days. The new Investigator must be approved by Sponsor and the IRB/IEC before the study can be continued.

If Sponsor and/or the Investigator should discover conditions arising during the study that indicate it should be terminated, an appropriate schedule for termination will be instituted. If the Investigator terminates the study, an explanatory letter will be provided to Sponsor.

Sponsor also reserves the right to discontinue this study for administrative reasons at any time. The Investigator will be reimbursed for reasonable expenses incurred, if it is necessary to terminate the study or an individual patient's participation. Sponsor will not reimburse the Investigator for the evaluation of patients if the evaluations are not conducted in compliance with the present protocol.

9.9. Information material

Before the beginning of the study the Investigator will be given the last updated IB. If the IB is revised during the study, the Investigator will receive a copy of the revised version. The IB and the protocol are confidential communications of Sponsor. Acceptance constitutes the agreement by the recipient that no unpublished information herein contained will be published or disclosed without Sponsor's prior written approval except that this document may be disclosed to an appropriate IRB/IEC as long as they are required to keep it confidential.

10.0 CONFIDENTIALITY

All information provided to the Investigator dealing with the study medication will be regarded as confidential. The members of the research team agree not to discuss such information in any way without prior written permission from Sponsor.

11.0 SIGNATURES OF SPONSOR AND INVESTIGATOR

A randomized, multicenter, phase II study of nab-paclitaxel plus gemcitabine versus gemcitabine for the first-line treatment of metastatic or locally advanced unresectable adenocarcinoma of the pancreas.

11.1. Declaration of Sponsor

This study protocol was subject to critical review and has been approved by the appropriate protocol review committee of the Sponsor. The information it contains is consistent with:

- The current risk-benefit evaluation of the investigational product
- The moral, ethical, and scientific principles governing clinical research as set out in the Declaration of Helsinki and the principles of ICH GCP.

The Investigator will be supplied with details of any significant or new findings, including AEs, relating to treatment with the investigational product.

Date:_____Signature: _____

11.2. Declaration of Investigator

I confirm that I have read the above protocol, appendices, and referenced documents. I understand the contents and intend to fully comply with all requirements. No changes will be made without formal authorization by Sponsor in the form of a protocol amendment. I will work according to the moral, ethical, and scientific principles governing clinical research as set out in the Declaration of Helsinki and the principles of ICH GCP.

I confirm that I am not banned from conducting clinical research and I will immediately contact Sponsor if I cannot fulfill my obligations to complete this protocol.

Investigator

Date:_____Signature _____

Name (block letters): _____

12.0 REFERENCES

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APPENDIX A

RESPONSE EVALUATION CRITERIA IN SOLID TUMORS (RECIST)

Quick Reference

Eligibility

Only patients with measurable disease at baseline should be included in protocols where objective tumor response is the primary endpoint.

Measurable disease - the presence of at least one measurable lesion. If the measurable disease is restricted to a solitary lesion, its neoplastic nature should be confirmed by cytology/histology.

Measurable lesions - lesions that can be accurately measured in at least one dimension with longest diameter ≥20 mm using conventional techniques or ≥10 mm with spiral CT scan.

Non-measurable lesions - all other lesions, including small lesions (longest diameter <20 mm with conventional techniques or <10 mm with spiral CT scan), ie, bone lesions, leptomeningeal disease, ascites, pleural/pericardial effusion, inflammatory breast disease, lymphangitis cutis/pulmonis, cystic lesions, and also abdominal masses that are not confirmed and followed by imaging techniques; and

- All measurements should be taken and recorded in metric notation, using a ruler or calipers. All baseline evaluations should be performed as closely as possible to the beginning of treatment and never more than 4 weeks before the beginning of the treatment.
- The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during follow-up.
- Clinical lesions will only be considered measurable when they are superficial (eg, skin nodules and palpable lymph nodes). For the case of skin lesions, documentation by color photography, including a ruler to estimate the size of the lesion, is recommended.

Methods of Measurement

- CT and MRI are the best currently available and reproducible methods to measure target lesions selected for response assessment. Conventional CT and MRI should be performed with cuts of 10-mm or less in slice thickness contiguously. Spiral CT should be performed using a 5-mm contiguous reconstruction algorithm. This applies to tumors of the chest, abdomen and pelvis. Head and neck tumors and those of extremities usually require specific protocols.
- Lesions on chest X-ray are acceptable as measurable lesions when they are clearly defined and surrounded by aerated lung. However, CT is preferable.
- When the primary endpoint of the study is objective response evaluation, ultrasound (US) should not be used to measure tumor lesions. It is, however, a possible alternative to clinical measurements of superficial palpable lymph nodes, subcutaneous lesions and thyroid nodules. Ultrasound might also be useful to confirm the complete disappearance of superficial lesions usually assessed by clinical examination.
- The utilization of endoscopy and laparoscopy for objective tumor evaluation has not

yet been fully and widely validated. Their uses in this specific context require sophisticated equipment and a high level of expertise that may only be available in some centers. Therefore, the utilization of such techniques for objective tumor response should be restricted to validation purposes in specialized centers. However, such techniques can be useful in confirming complete pathological response when biopsies are obtained.

- Tumor markers alone cannot be used to assess response. If markers are initially above the upper normal limit, they must normalize for a patient to be considered in complete clinical response when all lesions have disappeared.
- Cytology and histology can be used to differentiate between PR and CR in rare cases (eg, after treatment to differentiate between residual benign lesions and residual malignant lesions in tumor types such as germ cell tumors).

Baseline Documentation of "Target" and "Non-Target" Lesions

- All measurable and non-measurable lesions should be identified at baseline and at the stipulated intervals during treatment.
- One or two lesions will be defined as ***target lesion***. The target lesions should be selected on the basis of its size (lesions with the longest and second-longest diameter) and its suitability for accurate measurements by imaging techniques. The diameters will be recorded for the target lesions. The sum of the longest diameters as determined at baseline will be used as a reference to further characterize the objective tumor response during treatment.
- All other lesions (or sites of disease) should be identified as ***non-target lesions*** and should also be recorded at baseline. Measurements of these lesions are not required, but the presence or absence of each should be noted throughout follow-up.

Response Criteria

Evaluation of Target Lesion	
Complete Response (CR)	Disappearance of all target lesions for at least 4 weeks
Partial Response (PR)	At least a 30% decrease in the sum of the LD of target lesions, taking as reference the baseline sum LD for at least 4 weeks
Progressive Disease (PD)	At least a 20% increase in the sum of the LD of target lesions, taking as reference the smallest sum LD recorded since the treatment started or the appearance of one or more new lesions
Stable Disease (SD)	Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum LD since the treatment started for at least 6 weeks

Evaluation of Non-target Lesions	
Complete Response (CR)	Disappearance of all non-target lesions and normalization of tumor marker level for at least 4 weeks
Incomplete Response/ Stable Disease (SD)	Persistence of one or more non-target lesion(s) or/and maintenance of tumor marker level above the normal limits for at least 6 weeks
Progressive Disease (PD)	Appearance of one or more new lesions and/or unequivocal progression of existing non-target lesions.**

**Although a clear progression of “non target” lesions only is exceptional, in such circumstances, the opinion of the treating physician should prevail and the progression status should be confirmed later on by the review panel (or Study Chair).

Evaluation of Best Overall Response

The best overall response is the best response recorded from the start of the treatment until disease progression/recurrence (taking as reference for PD the smallest measurements recorded since the treatment started). In general, the patient's best response assignment will depend on the achievement of both measurement and confirmation criteria.

Target Lesions	Non-target Lesions	New Lesions	Overall Response
CR	CR	No	CR
CR	Incomplete Response/Stable Disease (SD)	No	PR
PR	Non-PD	No	PR
SD	Non-PD	No	SD
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD

- Patients with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be classified as having “symptomatic deterioration”. Every effort should be made to document the objective progression even after discontinuation of treatment.
- In some circumstances it may be difficult to distinguish residual disease from normal tissue. When the evaluation of complete response depends on this determination, it is recommended that the residual lesion be investigated (fine needle aspirate/biopsy) to confirm the complete response status.

Confirmation

- The main goal of confirmation of objective response is to avoid overestimating the response rate observed. In cases where confirmation of response is not feasible, it should be made clear when reporting the outcome of such studies that the responses are not confirmed.
- To be assigned a status of PR or CR, changes in tumor measurements must be confirmed by repeat assessments that should be performed no less than 4 weeks after the criteria for response are first met. Longer intervals as determined by the study protocol may also be appropriate.
- In the case of SD, follow-up measurements must have met the SD criteria at least once after study entry at a minimum interval (in general, not less than 6-8 weeks) that is defined in the study protocol.

Duration of Overall Response

- The duration of overall response is measured from the time measurement criteria are met for CR or PR (whichever status is recorded first) until the first date that recurrence or PD is objectively documented, taking as reference for PD the smallest measurements recorded since the treatment started.

Duration of Stable Disease

- SD is measured from the start of the treatment until the criteria for disease progression are met, taking as reference the smallest measurements recorded since the treatment started.
- The clinical relevance of the duration of SD varies for different tumor types and grades. Therefore, it is highly recommended that the protocol specify the minimal time interval required between two measurements for determination of SD. This time interval should take into account the expected clinical benefit that such a status may bring to the population under study.

Response Review

- For trials where the response rate is the primary endpoint it is strongly recommended that all responses be reviewed by an expert(s) independent of the study at the study's completion. Simultaneous review of the patients' files and radiological images is the best approach.

Reporting of Results

- All patients included in the study must be assessed for response to treatment, even if there are major protocol treatment deviations or if they are ineligible. Each patient will be assigned one of the following categories: 1) complete response, 2) partial response, 3) stable disease, 4) progressive disease, 5) early death from malignant disease, 6) early death from toxicity, 7) early death because of other cause, or 9) unknown (not assessable, insufficient data).
- All of the patients who met the eligibility criteria should be included in the main analysis of the response rate. Patients in response categories 4-9 should be considered as failing to respond to treatment (disease progression). Thus, an incorrect treatment schedule or drug administration does not result in exclusion from the analysis of the response rate. Precise definitions for categories 4-9 will be protocol specific.
- All conclusions should be based on all eligible patients.
- Subanalyses may then be performed on the basis of a subset of patients, excluding those for whom major protocol deviations have been identified (eg, early death due to other reasons, early discontinuation of treatment, major protocol violations, etc). However, these subanalyses may not serve as the basis for drawing conclusions concerning treatment efficacy, and the reasons for excluding patients from the analysis should be clearly reported.
- The 95% confidence intervals should be provided.

APPENDIX B
Declaration of Helsinki

Initiated: 1964 17.C Original: English

WORLD MEDICAL ASSOCIATION DECLARATION OF HELSINKI
Recommendations guiding physicians in biomedical research involving human subjects

Adopted by the 18th World Medical Assembly
Helsinki, Finland, June 1964
and amended by the
29th World Medical Assembly, Tokyo, Japan, October 1975
35th World Medical Assembly, Venice, Italy, October 1983
41st World Medical Assembly, Hong Kong, September 1989
and the
48th General Assembly,Somerset West, Republic of South Africa, October 1996

INTRODUCTION

It is the mission of the physician to safeguard the health of the people. His or her knowledge and conscience are dedicated to the fulfillment of this mission. The Declaration of Geneva of the World Medical Association binds the physician with the words, "The Health of my patient will be my first consideration," and the International Code of Medical Ethics declares that, "A physician shall act only in the patient's interest when providing medical care which might have the effect of weakening the physical and mental condition of the patient." The purpose of biomedical research involving human subjects must be to improve diagnostic, therapeutic and prophylactic procedures and the understanding of the aetiology and pathogenesis of disease. In current medical practice most diagnostic, therapeutic or prophylactic procedures involve hazards. This applies especially to biomedical research. Medical progress is based on research which ultimately must rest in part on experimentation involving human subjects. In the field of biomedical research a fundamental distinction must be recognized between medical research in which the aim is essentially diagnostic or therapeutic for a patient, and medical research, the essential object of which is purely scientific and without implying direct diagnostic or therapeutic value to the person subjected to the research. Special caution must be exercised in the conduct of research which may affect the environment, and the welfare of animals used for research must be respected. Because it is essential that the results of laboratory experiments be applied to human beings to further scientific knowledge and to help suffering humanity, the World Medical Association has prepared the following recommendations as a guide to every physician in biomedical research involving human subjects. They should be kept under review in the future. It must be stressed that the standards as drafted are only a guide to physicians all over the world. Physicians are not relieved from criminal, civil and ethical responsibilities under the laws of their own countries.

I. BASIC PRINCIPLES

1. Biomedical research involving human subjects must conform to generally accept scientific principles and should be based on adequately performed laboratory and animal experimentation and on a thorough knowledge of the scientific literature.
2. The design and performance of each experimental procedure involving human subjects should be clearly formulated in an experimental protocol which should be transmitted for consideration, comment and guidance to a specially appointed

committee independent of the investigator and the sponsor provided that this independent committee is in conformity with the laws and regulations of the country in which the research experiment is performed.

3. Biomedical research involving human subjects should be conducted only by scientifically qualified persons and under the supervision of a clinically competent medical person. The responsibility for the human subject must always rest with a medically qualified person and never rest on the subject of the research, even though the subject has given his or her consent.
4. Biomedical research involving human subjects cannot legitimately be carried out unless the importance of the objective is in proportion to the inherent risk to the subject.
5. Every biomedical research project involving human subjects should be preceded by careful assessment of predictable risks in comparison with foreseable benefits to the subject or to others. Concern for the interests of the subject must always prevail over the interests of science and society.
6. The right of the research subject to safeguard his or her integrity must always be respected. Every precaution should be taken to respect the privacy of the subject and to minimize the impact of the study on the subject's physical and mental integrity and on the personality of the subject.
7. Physicians should abstain from engaging in research projects involving human subjects unless they are satisfied that the hazards involved are believed to be predictable. Physicians should cease any investigation if the hazards are found to outweigh the potential benefits.
8 In publication of the results of his or her research, the physician is obliged to preserve the accuracy of the results. Reports of experimentation not in accordance with the principles laid down in this Declaration should not be accepted for publication.
9. In any research on human beings, each potential subject must be adequately informed of the aims, methods, anticipated benefits and potential hazards of the study and the discomfort it may entail. He or she should be informed that he or she is at liberty to abstain from participation in the study and that he or she is free to withdraw his or her consent to participation at any time. The physician should then obtain the subject's freely-given informed consent, preferably in writing.
10. When obtaining informed consent for the research project the physician should be particularly cautious if the subject is in a dependent relationship to him or her or may consent under duress. In that case the informed consent should be obtained by a physician who is not engaged in the investigation and who is completely independent of this official relationship.
11. In case of legal incompetence, informed consent should be obtained from the legal guardian in accordance with national legislation. Where physical or mental incapacity makes it impossible to obtain informed consent, or when the subject is a minor, permission from the responsible relative replaces that of the subject in accordance with national legislation. Whenever the minor child is in fact able to give a consent, the minor's consent must be obtained in addition to the consent of the minor's legal guardian.
12. The research protocol should always contain a statement of the ethical considerations involved and should indicate that the principles enunciated in the present Declaration are complied with.

II. MEDICAL RESEARCH COMBINED WITH PROFESSIONAL CARE (Clinical Research)

1. In the treatment of the sick person, the physician must be free to use a new diagnostic and therapeutic measure, if in his or her judgement it offers hope of saving life, reestablishing health or alleviating suffering.
2. The potential benefits, hazards and discomfort of a new method should be weighed against the advantages of the best current diagnostic and therapeutic methods.
3. In any medical study, every patient - including those of a control group, if any - should be assured of the best proven diagnostic and therapeutic method. This does not exclude the use of inert placebo in studies where no proven diagnostic or therapeutic method exists.
4. The refusal of the patient to participate in a study must never interfere with the physician-patient relationship.
5. If the physician considers it essential not to obtain informed consent, the specific reasons for this proposal should be stated in the experimental protocol for transmission to the independent committee (I, 2).
6. The physician can combine medical research with professional care, the objective being the acquisition of new medical knowledge, only to the extent that medical research is justified by its potential diagnostic or therapeutic value for the patient.

III. NON-THERAPEUTIC BIOMEDICAL RESEARCH INVOLVING HUMAN SUBJECTS (Non-Clinical Biomedical Research)

1. In the purely scientific application of medical research carried out on a human being, it is the duty of the physician to remain the protector of the life and health of that person on whom biomedical research is being carried out.
2. The subject should be volunteers - either healthy persons or patients for whom the experimental design is not related to the patient's illness.
3. The investigator or the investigating team should discontinue the research if in his/her or their judgement it may, if continued, be harmful to the individual.
4. In research on man, the interest of science and society should never take precedence over considerations related to the wellbeing of the subject

APPENDIX C

Flow Chart

Visits	Enrollment examination	Before each medication administration	Week 8 (days 50-56) Week 16 (days 106-112)	Final examination
	Baseline		With therapy	At Progression
Inclusion and exclusion criteria	X			
Patient consent	X			
Demographic data	X			
Anamnesis	X			
Chest X-ray	X			
Physical examination	X	Beginning of every new cycle		X
Blood samples	X	X		X
Urine status	X			X
Vital signs, weight, height	X	X		X
Tumor staging	X		X	X
ECG	X			
Toxicity determination	X	X		X
(S)AE / ADR documentation		X		X
Drugs dispensed	X	X		X
CA 19-9	X	Beginning of every new cycle		X
Quality-of-life	X		Week 4 and every 4 weeks thereafter	X
Exit questionnaire				X

APPENDIX D

Toxicity criteria: NCI-CTCAE version 4.0

CTC	1	2	3	4	5
Karnofsky ≥16 J. Lansky <16 J.	80-70% 80-70%	60-50% 60-50%	40-30% 40-30%	20-10% 20-10%	Death
Haemoglobin [g/l]	<LLN – 100	<100-80	<80-65	<65	Death
Leukocytes [Gpt/l]	<LLN - 3.0	<3.0-2.0	<2.0-1.0	<1.0	Death
Neutrophiles [Gpt/l]	<LLN - 1.5	<1.5-1.0	<1.0-0.5	<0.5	Death
Plateletes [Gpt/l]	<LLN – 75	<75-50	<50-25	<25	Death
Haemorrhage/Bleeding: ☐ Abdomen NOS ☐ Stomach ☐ Esophagus	Mild bleeding, no transfusion	Groos bleeding, 1-2 transfusion per episode	Severe, 3-4 transfusions per epsiode	Life-threatening, >4 transfusions per epsiode	Death
Skin/Exanthema	Rash/Erythema	Dry desquamation, mild Pruritis	Moist desquamations, ulcerations	Generalizied exfoliative/ulcerative or bullous dermatitis, necrosis	——
Infection	---------	Local, local intervention indicated	i.v.-Antibiotics, antimycotics or antiviral therapy indicated	Life-threatening (e.g. septic shock, hypotension, acidosis)	Death
Febrile neutropenia [Fever of unknown origin (FUO) ≥38.5°C, Neutrophiles <1.0 Gpt/l]	---------	----------	Existent	Life-threatening (e.g. septic shock, hypotension, acidosis)	Death
Fever [°C]	38 – 39	>39 – 40	>40 for <24 hrs.	>40 for >24 hrs.	Death
Nausea	Loss of appetite without alteration in eating habits	Oral intake altered without significant weight loss or malnutrition, oral nutritional supplements	No oral intake with significant weight loss, infusion, enterale nutrition or TPN >24 hrs.	Life-threatening TPN >24 hrs. indicated	Death

		indicated, dehydration or infusion <24 hrs.	indicated		
Vomiting/24 hrs.	1x/24 hrs.	2-5x/24 hrs., infusion <24 hrs.	>6x/24 hrs., infusion or TPN ≥24 hrs.	Life-threatening	Death
Stomatitis (oral cavity)/ Mucositis (lower gastrointestinal tract)	Erythema, mild pain, no interventions indicated	Patchy ulcerations or pseudomembranes, moderate pain, analgesics, no interfering with function	Confluent ulcerations or pseudomembranes, bleeding with minor trauma, severe pain, analgesics, infusion, interfering with function	Tissue necrosis, significant spontaneous bleeding, severe pain, infusion, TPE life-threatening	Death

CTC	**1**	**2**	**3**	**4**	**5**
Diarrhea/ Stool frequency	<4x/24 hrs. without alteration in daily habits	4-6x/24 hrs. infusion <24 hrs., mild pain without alteration in daily habits	≥7x/24 hrs. or incontinence or infusion >24 hrs., hospitalization, severe pain with alteration in daily habits	Life-threatening (e.g. haemodynamic collapse)	Death
Constipation	Occasional or intermittent symptoms, dietary, occasional use of stool softeners, laxatives or enema	Persistent symptoms with regular use of laxatives or enema indicated	Constipation with manual evacuation indicated, alteration in daily habits	Life-threatening (e.g.. obstruction, toxic megacolon)	Death
Creatinine i.S. [mg/dl]	>ULN – 1,5xULN	<1.5-3.0xULN	>3.0-6.0xULN	>6.0xULN	Death
Proteinuria [Stick]	1 +	2+ - 3+	4+	Nephrotic syndrome	Death
Haematuria	Microscopic	Macroscopic without coagulae	Macroscopic with coagulae	Transfusions indicated	Death
Creatinine Clearance (ml/min/1,73 m²)	60-89	40-59	20-39	≤19	
Bilirubin i.S.	>ULN – 1.5xULN	>1.5-3.0xULN	<3.0-10.0xULN	>10.0xULN	
SGOT/SGPT	>ULN - 2.5xULN	>2.5-5.0xULN	>5.0-20.0xULN	>20.0xULN	

Alkaline phosphatase	>ULN – 2.5xULN	>2.5-5.0xULN	>5.0-20.0xULN	>20.0xULN	

Pulmonary Toxicitiy Dyspnoe	Mild dyspnoe on exertion, but can walk 1 flight of stairs without stopping	Moderate dyspnoe on exertion, but unable to walk 1 flight of stairs without stopping	Severe dyspnoe with alteration in daily habits	Life-threatening Dyspnoe at rest; intubation/ventilator indicated	Death
Restrictive Cardiomyopathy	Asymptomatic, therapy not indicated	Asymptomatic, therapy indicated	Symptomatic cardiac failure, responsive to interventions	Life-threatening, refractory cardiac failure	Death
Echocardiography: Left ventricular systolic dysfunction	EF <60-50% SF <30-24%	EF <50-40% SF <24-15%	EF <40-20% SF <15%	EF <20%	Death
Ototoxicity	Asymptomatic threshold shift of 15-25 dB relative to baseline	Symptomatic, threshold shift of 25-90 dB relative to baseline, tinnitus, mild hypacusis	Symptomatic, adults: threshold shift of 25-90 dB relative to baseline, children: bilateral >20 dB hearing loss, tinnitus, severe hypacusis, need of hearing aids	Profound bilateral hearing loss (>90 dB in adults, indication for cochlear implant in children)	____
Neurology – Central Neurotoxicity	Mild somnolence or agitation	Somnolence or sedation interfering with function, disorientation, brief generalized seizure (controlled)	Obtundation or stupor, disorientation, hallucinations, seizures with altered consciousness (poorly controlled)	Life-threatening coma, seizure difficult to control, status epilepticus	Death
Neurology - Peripheral Neurotoxicity	Asymptomatic weakness, mild paraesthesia, loss of deep tendon reflexes, not interfering with function	Moderate motor or sensory alteration, paraesthesia, including tingling, interfering with function but not with daily habits	Severe motor dysfunction or sensory loss or paraesthesia interfering with function and daily habits	Disabling, paralysis life-threatening	Death

http-Address of NCI - Common-Terminology-Criteria Version 3.0/4.0:

http://www.nci.nih.gov/
http://ctep.cancer.gov/reporting/ctc.html

Abbreviations:

LLN	Lower Limit of Normal (according to the normal values in the investigator centre)
ULN	Upper Limit of Normal (according to the normal values in the investigator centre)
nd	not done
EF	ejection fraction
SF	left ventricular shortening fraction
TPN	total parenteral nutrition

Toxicity scales:

Grade 1 to 5 according to Common Terminology-Criteria for Adverse Events v4.0 **(CTCAE)** – related to complication during anti-cancer therapy (see also Chapter 8, Assessment of safety):

Grade 1	mild adverse event
Grade 2	moderate adverse event
Grade 3	severe adverse event
Grade 4	life-threatening or disabling adverse event (e.g. paresis)
Grade 5	death related to adverse event (death of therapy related complications)

Remarks:

The documentation of the toxicity (AE/ADR) will be performed on the AE-Log or in case of SAE/SADR on both the AE-Log and the SAE-Log (see also Chapter 8, Assessment of safety). The SAE-Log has to be faxed within 24 hours of a working day to the study headquarters/the principal investigator. In case of death or termination of the study it is necessary to fill out the CRFs for the exit visit, e.g. the last follow-up examinations, and to send a copy of them to the study headquarters.