Protocol amended version 3.0 – 08/06/2015

Randomized crossover trial to assess the effects and quality of life in patients with locally advanced or metastatic pancreatic cancer treated with gemcitabine in combination with *nab*-paclitaxel: QOLINPAC

EudraCT # 2013-004101-75, U.Z. Leuven reference # S56122

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Academic study

sponsored by: U.Z. Leuven (University Hospital Leuven) · Herestraat 49 · B -3000 Leuven
supported by: Celgene International sarl · Route de Perreux 1 · 2017 Boudry · Switzerland · www.celgene.eu
Celgene IIT code #: AX-CL-PANC-PI-003568
This study is listed on www.clinicaltrials.gov

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1 Summary information

1.1 Coordinating center

U.Z. Leuven (University Hospital Leuven)
Digestive Oncology Unit
Herestraat 49
B-3000 Leuven
Belgium

1.2 Participating centers and local investigators

Belgian medical centers are selected based on experience. Details will be available at the time of submissions.

1.3 Writing committee

Dr. Gabriela Chiritescu
Prof. Dr. Eric Van Cutsem
Prof. Dr. Chris Verslype
Prof. Dr. Hans Prenen
Ms. Kristien Dumon

1.4 Patient registration online

The electronic platform is created by Lambda+: www.lambdaplus.com

Online registration address: https://www.qolinpac.net

Instructions are provided in the manual of procedures (MOP) and its appendices or by the clinical trial monitor.

1.5 Pharmacovigilance

The pharmacovigilance procedures and regulatory reporting are ensured by the CRO "The Clinical Company": http://www.theclinicalcompany.com

Instructions for serious adverse event reporting are provided in the protocol, the manual of procedures (MOP) and its appendices or by the clinical trial monitor.

1.6 Protocol signature sheet

I agree to conduct the study in accordance with the protocol and its amendment and in compliance with Good Clinical Practice and applicable regulatory requirements.

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Date:…….. Signature:…….

This document has been approved electronically. Additionally, a print-out of the document has been signed by the responsible persons and the original archived for regulatory purposes. A scanned copy of the signature sheet is attached to the protocol.

1.7 Study administrative structure

The U.Z. Leuven, Belgium is the sponsor of this investigator initiated clinical study with *nab*-paclitaxel. The study will take place under the umbrella of BGDO (Belgian Group of Digestive Oncology). Celgene EU is supporting the study by providing the investigational drug (*nab*-paclitaxel) and a research grant.

Selected centers in Belgium will participate. The central principal investigator will be Prof. Dr. E. Van Cutsem, U. Z. Leuven, Belgium.

Study coordination and study management will be performed by the sponsor and delegates.

Electronic data capture systems and case report forms will be developed by Lambda+ under the supervision of the sponsor.

Data management and statistical analysis of all data gathered in electronic case report forms will be performed by the sponsor and delegates. Statistical analysis of translational data will be performed by the sponsor.

Pharmacokinetic evaluations are not foreseen.

Quality of life parameters will be measured using the EORTC QLQ-C30 core questionnaire. Quality of life analysis will be performed by U.Z. Leuven following the EORTC guidelines.

Under the supervision of the sponsor, the appointed Clinical Research Organisation (CRO) or designated representatives will undertake the procedures related to drug safety and the timely reporting of Adverse Events (AEs), Serious Adverse Events (SAEs) and Suspected Unexpected Serious Adverse Reactions (SUSARs) as required. Safety data from the study will be processed as per current guidelines by the sponsor or delegates. All parties (Sponsor, Celgene and investigators) will receive and review the safety data on a regular basis as required by law in order to ensure that the continuation of the study is not to the detriment of the subjects.

The study medication will be produced under Good Manufacturing Practice (GMP) conditions. Distribution of study medication to all participating centers will be done by Celgene and appointed delegates.

Quality Assurance activities and data monitoring are performed and/or coordinated by the sponsor and delegates.

This study requires a logistical and administrative structure for its efficient execution. Details of such structures and associated procedures will be defined in the manual of procedures (MOP) prepared by the sponsor.

The following items will be addressed in the MOP and its appendices:

- Randomization and online registration of patients.
- Ordering, handling and preparation of study medication.
- Guidance for Case Report Form (e-CRF) and questionnaire completion.
- Reporting of SAEs.
- Translational research procedures: Instructions for collection, processing, storage and transportation of biological samples.
- Quality Assurance requirements.

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5-FU – 5 fluorouracil
ADR – adverse drug reactions
AE – adverse event
ALAT – alanine aminotransferase
ASAT – aspartate aminotransferase
BSA – body surface area
CA19-9 – carbohydrate antigen 19-9

CEA – carcinoembryonic antigen
CHMP – EMA's Committee for Medicinal Products for Human Use
CI – confidence interval
CoRs – certificate of release
CR – complete response
CRF – case report form
CRO – clinical research organisation
CRP – C-reactive protein
CT – computerized axial tomography
CTCAE – Common Terminology Criteria for Adverse Events
dCK – deoxyctine kinase
DNA – deoxyribonucleic acid
EC – ethics committee
ECG – electrocardiogram
ECOG – Eastern Cooperative Oncology Group
e-CRF – electronic case report form
EGFR – epidermal growth factor receptor
EMA – European Medicines Agency
EMT – epithelial - mesenchymal transition
EORTC – European Organization for Research and Treatment of Cancer
EOT – End of treatment
EUS – endoscopic ultrasound
FDA – U.S. Food and Drug Administration
FFPE – formalin fixed paraffin embedded
FOLFIRINOX– 5-FU+LV+Irinotecan+Oxaliplatin
G, GEM – gemcitabine
GCP – Good Clinical Practice
G-CSF – Granulocyte-Colony Stimulating Factor
GHS – Global Health Score
GMP – good manufacturing practice
hENT1 – Human equilibrative nucleoside transporter 1
HUS – Hemolytic uremic syndrome
HR – hazard ratio
IB – investigator brochure
IV– intravenous
ICH – International Conference on Harmonization
ISF – investigator site file
IST – investigator sponsored trials
ITT – intent to treat
LD – longest diameter
LDH – lactate dehydrogenase
LV – Leucovorin
MAH – Marketing Authorisation Holder
MOP – Manual of Procedures

MRI – magnetic resonance imaging
MTD – maximum tolerated doses
NC – no change
NCI – National Cancer Institute
NE – non evaluable
nP – *nab*-Paclitaxel
OR – odds ratio
OS – overall survival
PCR – polymerase chain reaction
PD – progressive disease
PFS – progression free survival
PI – principal investigator
PR- partial response
PS – performance status
Pt(s) – patient(s)
RECIST – Response Evaluation Criteria in Solid Tumours
RNA – ribonucleic acid
RR – response rate
RT – radiotherapy
SAE – serious adverse event
SAP – statistical analysis plan
SD – stable disease
SmPC – Summary of Product Characteristics
SPARC – secreted protein acidic and rich in cysteine
SUSAR – suspected unexpected serious adverse reactions
QOL – quality of life
TNM – tumour-nodes-metastasis
TR – translational research
TUDD – Time Until Definitive Deterioration
UAR – unexpected adverse reaction
ULN – upper limit of normal
WHO – World Health Organisation

1.13 Protocol synopsis

Study Acronym	QOLINPAC
EUDRACT No.	2013-004101-75
Local study No.	S56122
Study Design	Phase II, two arm, comparative, randomized, crossover, open label, multicenter.
Patient Population	Patients with metastatic or unresectable locally advanced pancreatic adenocarcinoma cancer histologically or cytologically confirmed, eligible for treatment with gemcitabine and *nab*-paclitaxel in a first line setting.
Study Sponsor	This is an investigator initiated academic study **Sponsor:** U.Z. Leuven (University Hospital Leuven) Digestive Oncology Unit Herestraat 49 B-3000 Leuven Belgium
Central principal investigator	Prof. Dr. Eric Van Cutsem
Countries, Investigators & Centers	Belgian centers with experience in clinical research are selected.
Study treatment	***Nab*-paclitaxel (Abraxane®)** Provided by: Celgene Formulation: 100 mg vials (5 mg/ml) Route: iv Dose & treatment mode: 125 mg/m^2 infusion over 30 min **Gemcitabine (Gemzar®)** On prescription (standard indication and dose) Formulation: 1000 or 2000 mg vials Route: iv Dose & treatment mode: 1000 mg/m^2 infusion over 30 min, after *nab*-paclitaxel Patients will be randomized to one of the following treatment regimens: **Arm A:** *Nab*-paclitaxel 125 mg/m² administered in combination with gemcitabine 1000 mg/m² weekly for 3 weeks followed by one week of rest (4 week cycles) OR **Arm B:** Gemcitabine, 1000 mg/m² administered weekly for 7 weeks followed by a week of rest (Cycle 1 is 8 weeks), followed by weekly administrations for 3 weeks followed by a week of rest (from Cycle 2 onward, 4 week cycles) Patients progressing in the gemcitabine alone arm are allowed to cross-over to the combination arm with *nab*-paclitaxel if eligibility is respected. Premedication is not necessary for nab-paclitaxel, however premedication with standard anti-emetics is recommended for gemcitabine and is to be administered prior to the infusion of nab-paclitaxel (in Arm A) and prior to the infusion of gemcitabine (in Arm B).

Treatment duration	Until disease progression or death, toxicity or withdrawal of consent (median duration expected on treatment of 4 cycles/months).
Translational research – samples, timepoints and analyses	**Blood** Type of samples: whole blood, plasma, serum Timepoints: ▪ Baseline ▪ W9 ▪ Progression or end of treatment for patients discontinued for other reason that progression or death. ▪ 2nd progression in cross-overs **Tissue** Type of samples: Previously archived formalin fixed paraffin embedded (FFPE) samples from biopsy in block or minimum 15 slides. Cytology (smear) is not acceptable. If not available, tissues can be collected by core needle biopsy (US guided, preferably endoscopic or percutaneous) in consenting patients. Paraffin block embedded at site. Timepoints: Baseline only. Analyses: ▪ Potential SNPs that can be related with benefit to *nab*-paclitaxel ▪ Circulating DNA ▪ Circulating micro-RNA ▪ Selected cytokines (ELISA) ▪ hENT1, SPARC, dCK and S100A2 expression and correlation with outcome (immunohistochemistry/qPCR) ▪ Hypoxia studies
Inclusion and exclusion criteria	**Inclusion criteria** 1. Written informed consent (+ optional for TR) must be given according to ICH/GCP and national/local regulations. 2. Patient is at least 18 years of age[1]. 3. Unresectable locally advanced or metastatic pancreatic cancer. 4. Histologically or cytologically confirmed adenocarcinoma of the pancreas. Islet cell neoplasms and neuroendocrine tumours are excluded. 5. Evaluable or measurable disease, not in a previously irradiated area. 6. Life expectancy of at least 12 weeks. 7. WHO ECOG performance status (PS) ≤ 2 8. Adequate organ function. 9. Adequate bone marrow, hepatic and renal function: a. Hemoglobin ≥ 8.0 g/dL, absolute neutrophil count ≥ 1.5 x 10^9/L, platelet count ≥ 100 x 10^9/L b. ALAT, ASAT ≤ 2.5 x ULN, up to ≤ 5 x ULN in case of liver involvement c. Total bilirubin ≤ 2 x ULN. No jaundice. d. Serum creatinine ≤ 1.5 x ULN and /or calculated creatinine clearance ≥ 60 mL/min (calculated according to Cockcroft and Gault). 10. Acceptable coagulation determined on routine tests (e.g. prothrombin time, partial thromboplastin time, INR, etc, within +/- 15% of normal limits or as per

[1] Patients with pancreatic adenocarcinoma aged 75 years and older should be carefully assessed for their ability to tolerate *nab*-paclitaxel in combination with gemcitabine with special consideration to performance status, co-morbidities and increased risk of infections.

<table>
<tr><td></td><td colspan="2">clinical practice).
11. No clinically significant abnormalities in urinalysis.
12. Effective contraception for both male and female patients if applicable. Women of childbearing potential must have negative blood pregnancy test at screening visit.

Exclusion criteria
1. Prior chemotherapy, surgery or other investigational therapy for the treatment for metastatic disease. Adjuvant treatment with gemcitabine or 5-FU is allowed provided at least 6 months have elapsed since completion of the last dose.
2. Major surgery within 4 weeks of the start of the study.
3. Irradiation within 3 weeks prior to study entry.
4. Brain metastasis (known or suspected).
5. Serious medical risk factors involving any of the major organ systems, including high cardiovascular risk including coronary stenting or myocardial infarction in the last year and psychiatric disorders.
6. Known infection with HIV or active infection with hepatitis B or C.
7. History of connective tissue disorders (eg. lupus, scleroderma, arteritis nodosa, etc).
8. History of interstitial lung disease.
9. History of peripheral artery disease
10. Previous (within 5 years) or concurrent malignancies at other sites with the exception of surgically cured or adequately treated carcinoma in-situ of the cervix and basal cell carcinoma of the skin.
11. Known allergy or any other adverse reaction to any of the drugs or to any related compound.
12. Use of oral anticoagulants that interfere with the metabolic path of nab-Paclitaxel (cytochrome P450 isoenzymes CYP2C8 and CYP3A4) such as warfarin (Coumadin), rivaroxaban (Xarelto), etc, and the impossibility to switch anticoagulation treatment to low molecular weight heparin.
13. Organ allografts requiring immunosuppressive therapy.
14. Pregnancy or breast-feeding.
15. Medical, social or psychological condition which, in the opinion of the investigator, would not permit the patient to complete the study or sign meaningful informed consent.

NB: See protocol for the timing of screening evaluations.</td></tr>
<tr><td>Arm allocation and cross-over</td><td colspan="2">Randomization will be performed in a 1:1 ratio performed by the electronic platform at patient registration (automated block randomization by center, performance status 0-1 vs. 2, tumour localization head vs. other, locally advanced vs. metastatic).
Patients progressing on gemcitabine alone are allowed to cross-over to the combination arm provided they still fulfill the eligibility criteria and no impeding toxicity or deterioration have occurred.</td></tr>
<tr><td>Study Objectives & Endpoints</td><td><u>Primary Objective</u>
To compare quality of life scores and times to definitive deterioration in patients receiving nab-paclitaxel + gemcitabine versus gemcitabine alone using the EORTC QLQ-C30 questionnaire.</td><td><u>Primary Endpoint</u>
Time Until Definitive Deterioration (TUDD) is defined as the time from randomization to the first observation of a definitive deterioration of a quality of life score.

The primary endpoint is the deterioration free rate at 3 months (% of patients free from definitive deterioration as defined</td></tr>
</table>

		above) – minimal clinically important difference (MCID) between global health scores from baseline is 10 points. The QOL questionnaire EORTC QLQ-C30 (Aaronson, et al., 1993) will be applied at baseline, then every four weeks (on day 1 of each cycle) for up to 12 months in all surviving patients, even in case of treatment discontinuation. The QOL scores will be calculated following the EORTC recommendations for scoring and statistical interpretation as in the EORTC QLQ-C30 Scoring Manual (Fayers, et al., 2001). All scales and scores of the questionnaire (global health, functional, symptoms) will be considered. The differences between treatment arms will be assessed using a time to event analysis methodology (Kaplan-Meier) and log rank tests.

	<u>Secondary Objectives</u>
	To evaluate in both treatment Arms:
	▪ Safety and tolerability profile (NCI-CTCAE v. 4.0)
	▪ Overall response and duration of response as assessed by imaging (RECIST 1.1) and tumour markers
	▪ Disease control rates
	▪ Progression free survival (PFS) and overall survival (OS)
	▪ Changes in serum CA 19-9 and CEA and composite index CA19-9xCEA
	▪ Exploratory biomarker and hypoxia studies on blood products and tumour tissues with possible correlations with efficacy outcomes.
		<u>Secondary Endpoints</u>
		▪ Descriptive safety; incidence of treatment-emergent toxicities in both Arms and incidence of dose modifications, interruptions and discontinuations.
		▪ Dose density and dose intensity.
		▪ Response and disease control rates - response evaluation will be performed every 8 weeks according to RECIST criteria (CT/MRI scan)
		▪ Duration of response
		▪ PFS
		▪ OS
		▪ Evolution of the levels of carbohydrate antigen 19-9 (CA19-9) on treatment (q 8 weeks) and composite index.
		▪ Biomarkers that can be related with benefit to *nab*-paclitaxel:
		  ▪ Potential SNPs
		  ▪ Circulating DNA
		  ▪ Circulating micro-RNA
		  ▪ Selected cytokines (ELISA)
		  ▪ hENT1, SPARC, dCK and S100A2 expression (immunohistochemistry/qPCR)
		  ▪ Hypoxia studies

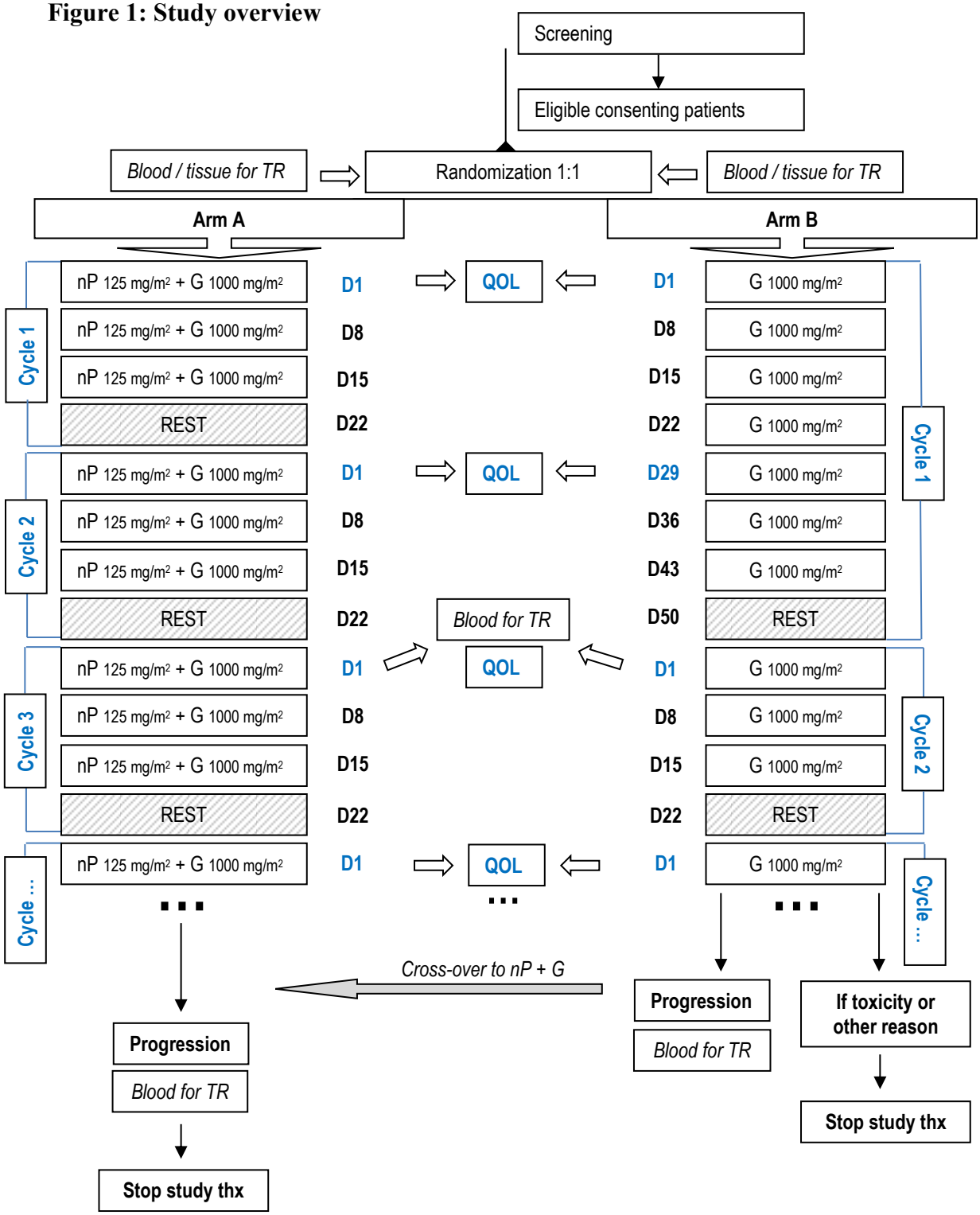
Statistical design parameters	**Rationale and methodology:** Primary objective: to compare patient reported outcomes (QOL scores) in patients receiving *nab*-paclitaxel + gemcitabine vs gemcitabine alone using the QOL Questionnaire C30 (EORTC QLQ-C30). Time Until Definitive Deterioration (TUDD) is defined as the time from baseline to the first observation of a definitive deterioration of a QOL score. Primary endpoint: 3-month deterioration free rate (TUDD) (% patients free from definitive deterioration at 3 months).	

	The sample size calculation is based on the global health score (GHS) 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. The hypotheses for sample size calculations are based on the results of the QOL analysis of the PRODIGE/ACCORD 11 trial (Gourgou-Burgade, et al., 2013). In this publication, the curves of TUDD of the global health score comparing folfirinox and gemcitabine show that the percentages of patients free from definitive deterioration at 3 months are 83% in Folfirinox Arm and 69% in gemcitabine Arm. Assuming similar results for the *nab*-paclitaxel with gemcitabine versus gemcitabine alone, these percentages are used as hypotheses for sample size calculations for the present study. A 3-month deterioration free rate of 83% for *nab*-paclitaxel + gemcitabine Arm and of 69% for gemcitabine Arm are assumed for calculating the sample size using a log-rank test. **Statistical assumptions for sample size calculation:** Hypotheses : a. 2-sided alpha=0.05 b. power=80% c. accrual 8-9 pts per month d. 3-months deterioration free rate of 83% for *nab*-paclitaxel + gemcitabine e. 3-months deterioration free rate of 69% for gemcitabine monotherapy Results: a. Accrual duration: 12-14 months b. Total study duration 21 months c. Total sample size N=100 d. Number of events E=68 (number of patients with definitive deteriorations) The drop-out rate is defined as the proportion of patients that failed to provide at least one QOL questionnaire at the end of treatment. We assume a 30% drop-out rate at the end of study which is in line with current EORTC recommendations on QOL studies. To reach the number of events estimated at point d. of the sample size calculation above and considering a 70% patient compliance in providing post-treatment QOL data (30% drop-out rate) an increase of the initial sample size to 143 patients (100/0.7=142.86 =~143) is required for reaching the main endpoint of the study. Randomization will be performed in a 1:1 ratio. Cross-over to *nab*-paclitaxel + gemcitabine is allowed after progression in the gemcitabine monotherapy Arm. Assessment of the EORTC QLQ-C30 questionnaire version 3 will be performed at baseline and subsequently every 4 weeks for up to 12 months in surviving patients. TUDD, with the use of a 10-point minimal clinically important difference, will be analyzed with the use of the Kaplan-Meier method and the log-rank test. Changes in mean scores per domain will be presented. Imaging by CT or MRI will be performed every 8 weeks. Overall survival and progression-free survival will be estimated with the use of the Kaplan-Meier method. No formal statistical comparisons will be performed between the two Arms on secondary endpoints. Results will be presented using descriptive statistics. Safety interim analyses are foreseen every six months. Several subgroup analyses are planned, by Arm and thx cross-over, demographic factors, disease characteristics, etc. Translational research studies will be performed by U.Z. Leuven.

Study Timelines	▪ Protocol finalized: Q4 2013 ▪ Submissions: Q1 2014 ▪ First patient in: Q2 2014 ▪ ▪ Last patient in: Q3 2015 ▪ Interim analysis for safety at 1 year ▪ Last patient off treatment: Q1 2016 ▪ Database lock: Q3 2016 ▪ Start of analysis: Q3 2016 ▪ Study report: Q1 2017

1.14 Study overview

Figure 1: Study overview



The QOL questionnaire (EORTC QLQ-C30) is applied at baseline and then every 4 weeks for up to 12 months.

TR: Blood samples for translational research are required at baseline, after 8 weeks on treatment (2 cycles Arm A and 1 cycle Arm B), at cross-over (if applicable) and at progression. Previously archived tissue samples available or samples collected by core needle biopsy from consenting patients are required at baseline.

Tumour evaluations by CT or MRI scan are performed every 8 weeks until progression then routine practice.

Tumour markers CA19-9 and CEA are measured every 8 weeks at the time of tumour evaluations.

2 Background and rationale

2.1 Pancreatic cancer

In 2012 there were 78,700 new cases of pancreatic cancer in Europe with an estimated number of 77,900 deaths from the disease (Ferlay, et al., 2013). At diagnosis, most patients are inoperable and present with advanced disease, as a result of the lack of specific symptoms while the disease develops. Patients with advanced disease are usually treated with chemotherapy, with the intent of prolonging survival and palliate symptoms (pain, weight loss and decrease in performance status).

Median survival time ranges from 4 to 6 months in patients with metastatic disease. Overall, the 5-year survival rate is about 4% for all stages combined and decreases to 1.6% for patients with metastatic pancreatic cancer.

Since 1997, gemcitabine has become the standard chemotherapy for treatment of advanced pancreatic cancer, after demonstration in a comparative study between gemcitabine and 5-fluorouracil (5-FU), that gemcitabine produced significant improvement in disease-related symptoms and prolonged survival (1-year survival: 18% versus 2%, respectively) (Burris, et al., 1997). In that study, median survival was 5.65 months for gemcitabine-treated patients and 4.41 months for 5-FU treated patients, while overall tumour response, as assessed by RECIST was 5.4% and 0%, respectively.

Moore and collaborators (Moore, et al., 2007) reported that the addition of erlotinib (an oral epidermal growth factor inhibitor) to gemcitabine, improved median overall survival (OS) (6.24 months for the doublet vs. 5.91 months for gemcitabine alone), 1-year survival (23% vs. 17%, respectively) and progression free survival (PFS) [Hazard ratio (HR) 0.77 in favor of the doublet], all without a significant difference in objective response rates between the study Arms.

Since then, some trials of newer cytotoxic or biologic agents combined with gemcitabine have not shown significant survival improvement compared with gemcitabine alone (Silvestris, et al., 2013). The addition of bevacizumab to gemcitabine-erlotinib did not lead to a statistically significant improvement in OS in patients with metastatic pancreatic cancer. PFS was longer in the bevacizumab group (Van Cutsem, et al., 2009).

The use of FOLFIRINOX regimen (5-FU+LV+Irinotecan+Oxaliplatin) has demonstrated efficacious results (Conroy, et al., 2011), (Conroy, Gavoille, Samalin, Ychou, & Ducreux, 2013). The median OS was 11.1 months in the FOLFIRINOX group as compared with 6.8 months in the gemcitabine group (HR for death, 0.57; $P<0.001$). Median PFS was 6.4 months in the FOLFIRINOX group and 3.3 months in the gemcitabine group (HR for disease progression, 0.47; $P<0.001$). The objective response rate was 31.6% in the FOLFIRINOX group versus 9.4% in the gemcitabine group ($P<0.001$). More adverse events were noted in the FOLFIRINOX group; 5.4% of patients in this group had febrile neutropenia. At 6 months, 31% of the patients in the FOLFIRINOX group had a definitive degradation of the quality of life versus 66% in the gemcitabine group (HR 0.47; $P<0.001$). Significant toxicity of the FOLFIRINOX regimen in this setting limits its administration exclusively to subjects with good performance status.

The improvements in patient outcomes have been rather modest with existing or experimental treatments so far and new solutions are therefore needed in advanced pancreatic cancer.

2.2 Response assessments in pancreatic cancer

Unlike other solid tumours, where imaging provides an accurate and reliable means to assess tumour size, pancreatic cancer might pose difficulties in lesion measurements and response assessments due to the desmoplastic component of the lesions. If the lesion is mostly desmoplastic, successful therapy can result in minimal change in measurement (Tempero, 1997). For this reason, there is increasing interest in identifying alternative endpoints with which to evaluate effective therapy.

A biological marker widely used in clinical practice in the assessment and follow-up of patients with pancreatic cancer is the carbohydrate antigen 19-9 (CA19-9). Serial measurements of CA19-9 are frequently performed for prognostic purposes, for following disease relapse and activity, and for monitoring patients undergoing therapy. The use of CA19-9 biomarker as surrogate endpoint in clinical trial design has not been universally established. However, a strong correlation between marker decline during chemotherapy and patient outcomes has been observed (Ko, Hwang, Venook, Abbruzzese, Bergsland, & Tempero, 2005), (Wong, Ko, Hwang, Venook, Bergsland, & Tempero, 2008), (Boeck, Stieber, Holdenrieder, Wilkowski, & Heinemann, 2006), (Poruk, et al., 2013), (Haas, et al., 2013) and a recommendation has been made to use this biomarker as a surrogate endpoint in clinical trials in pancreatic cancer (Ko, Hwang, Venook, Abbruzzese, Bergsland, & Tempero, 2005) (Wong, Ko, Hwang, Venook, Bergsland, & Tempero, 2008). The remarkable CA19-9 decreases seen in the Celgene sponsored CA040 study in pancreas (Von Hoff, et al., 2011) justify the evaluation of changes in this biomarker in our proposed study as a surrogate indicator for efficacy. Expression and correlation with efficacy outcomes will be explored in this trial as secondary endpoint.

Furthermore, newer studies have shown that a composite index of CA19-9 and CEA (carcinoembryonic antigen) is a stronger prognostic biomarker than each marker alone (Kanda, et al., 2013), (Distler, Pilarsky, Kersting, & Grützmann, 2013). The variation of the composite index CA19-9xCEA on treatment will also be explored in our study.

The secreted protein acidic and rich in cysteine (SPARC) expression impacts proliferation and apoptosis in different solid tumours: ovarian, lung, cervix, hepatocellular carcinoma, gastric and others. Furthermore, *nab*-Paclitaxel has shown antitumour activity in some other advanced cancer types that overexpress SPARC including breast (Watkins, Douglas-Jones, Bryce, Mansel, & Jiang, 2005), (Gradishar, et al., 2005), (Lobo, Lopes, Silva, & al, 2007), (Yardley, Daniel, Inhorn, & al, 2010), lung (Koukourakis, Giatromanolaki, Brekken, & al, 2003), (Socinski, Manikhas, Stroyakovsky, & al, 2010), (Socinski, Bondarenko, Karaeva, & al, 2011) and melanoma (Massi, Franchi, Borgognoni, & al, 1999), (Hersh, O'Day, Ribas, & al, 2010). In an analysis of specimens from patients with pancreatic cancer, SPARC was noted to be overexpressed in 13/16 (81%) of cases analysed (Von Hoff, Penny, Shack, & al, 2006). A significant increase in OS was observed for patients in the high-SPARC group compared with patients in the low-SPARC group (median OS, 17.8 v 8.1 months, respectively; P = .0431). Furthermore, SPARC level remained a significant predictor for the OS in a multivariate analysis correcting for confounding factors in the same study. Specifically, stromal SPARC was significantly correlated with OS (P = .013), but not SPARC in tumour cells (P = .15). (Von Hoff, et al., 2011). These observations warrant further investigations of the hypothesis that stromal SPARC expression may be an important marker of early activity of gemcitabine plus nab-paclitaxel combination regimens in advanced pancreatic cancer.

As in other disease settings, identification of predictive biomarkers for future development of new targeted agents active in pancreatic cancer must become a priority for clinical trials. Several signalling pathways targets are under investigation (VEGF/EGFR, IGF-1R, MMPs,

Hedgehog proteins, m-TOR, MEK, COX-2, etc.) (Silvestris, et al., 2013) and provide the rationale for own molecular exploratory analyses.

2.3 Quality of Life measures in pancreatic cancer

Quality of life (QOL) measures have been performed in cancer populations (advanced lung, brain, pancreas, breast) in an attempt to characterize surrogate endpoints for progression free survival and overall survival or determine the prognostic value of patient self-reported outcomes on different health or general QOL domains. A literature review of studies published between 1982 and 2008 (Montazeri, 2009) provides the evidence for a positive relationship between quality of life data or some quality of life measures and the survival duration of cancer patients.

Most of the recent studies have used the European Organization for Research and Treatment of Cancer (EORTC) QLQ-C30 quality of life questionnaire, a validated cancer specific instrument with precise scoring and interpretation methodology (Aaronson, et al., 1993), (Fayers, et al., 2001) which ensured reproducibility in different settings and the ability to consolidate the existing data from specific patient populations.

A meta-analysis of randomized trials by EORTC including 7417 patients with cancer who filled the baseline QLQ-C30 questionnaire (Quinten, et al., 2009) revealed that scores on the physical, pain and anorexia domains were significant prognostic variables for survival in addition to age, gender and distant metastases. A more recent publication of the same quality of life research group at EORTC concludes that in pancreatic cancer the baseline global health status was predictive for survival (Quinten, et al., 2013).

Several other published QOL studies performed in pancreatic cancer indicated that QOL scores at baseline and their evolution on treatment might improve the estimation of survival probability when added to clinical and demographic variables (Gourgou-Burgade, et al., 2013), (Braun, Gupta, & Staren, 2013). A study estimating prognosis in advanced pancreatic cancer based on the tumour maker CA19-9 and QOL indicators (Bernhard, et al., 2010) showed that pain and fatigue are independent prognostic factors for survival.

Our study will use the EORTC QLQ-C30 questionnaire to undertake a thorough analysis of each QOL domain in our target population. We aim to demonstrate the importance of patient self-reported health related QOL variables in the prognostic of advanced and metastatic pancreatic cancer and bring complementary QOL information on the effects of the combination *nab*-paclitaxel/gemcitabine on patients' quality of life.

2.4 Gemcitabine

Gemcitabine (Gemzar® Eli Lilly[2]) is a pyrimidine antimetabolite and is metabolised intracellularly by nucleoside kinase to the active diphosphate and triphosphate nucleosides. The cytotoxic effect of gemcitabine is due to inhibition of the DNA synthesis (masked chain termination). After incorporation into DNA, gemcitabine appears to induce the programmed cell death.

Gemcitabine is approved in Europe in different indications in solid tumours: bladder cancer, advanced non-small cell lung cancer, locally advanced or metastatic pancreatic cancer, breast cancer and ovarian cancer.

In locally advanced pancreatic cancer gemcitabine is standard of care at 1000 mg/m^2, given by 30-minute intravenous (iv) infusion, repeated once weekly for up to 7 weeks followed by

[2] Generics produced by several pharmaceutical companies are now available.

a week of rest. Subsequent cycles should consist of injections once weekly for 3 consecutive weeks out of every 4 weeks.

2.5 Paclitaxel

Paclitaxel is an anti-microtubule agent that has a broad spectrum of activity against human cancers by stabilizing intracellular microtubules by blocking molecular depolymerisation (Abraxis BioScience, Celgene Corporation, 2013, p. 19). This stability results in the inhibition of the normal dynamic reorganization of the microtubule network that is essential for vital interphase and mitotic cellular functions. In addition, paclitaxel induces unusually unstable tubulin complexes and abnormal arrays or "bundles" of microtubules throughout the cell cycle which interfere with mitosis resulting in cell death.

Paclitaxel was first authorized as Taxol® (Bristol-Myers Squibb) and is now available as generic equivalents. Taxol consists of paclitaxel dissolved in a proprietary solvent (Cremophor® EL (BASF) and ethanol.

Taxol, together with other taxanes, is routinely used for treatment of breast and lung cancers, melanomas and other solid tumours.

2.6 Paclitaxel albumin-bound particles (*nab*-paclitaxel, Abraxane®, ABI-007)

Nab-paclitaxel is a unique protein formulation of a non-crystalline, amorphous form of paclitaxel in an insoluble particle state. *Nab*-paclitaxel has been developed to improve the therapeutic index of paclitaxel (Taxol), also reducing the toxicities associated with Taxol, the Cremophor EL and the ethanol vehicle.

Conditions which are responsive to paclitaxel such as non-hematological solid tumour malignancies are good clinical candidates for treatment with *Nab*-paclitaxel. *Nab*-paclitaxel alone and in combination has been evaluated in a number of cancers including metastatic melanoma, non-small cell lung cancer, pancreatic cancer, and other solid tumours.

Nab-paclitaxel is approved globally (42 countries) for the treatment in different settings and lines of metastatic breast cancer based on the results of the phase III study CA012-0, (Abraxis BioScience, Celgene Corporation, 2013, p. 16), which demonstrated greater efficacy of *nab*-paclitaxel compared to Taxol. Additionally, *nab*-paclitaxel is approved in the United States for the first-line treatment of locally advanced or metastatic non-small cell lung cancer (NSCLC) in combination with carboplatin based on the results of the phase III study CA031, (Abraxis BioScience, Celgene Corporation, 2013, p. 16).

Nab-paclitaxel was approved by the U.S. Food and Drug Administration (FDA) for the treatment of locally advanced and metastatic pancreatic cancer in September 2013 based on the results of the CA046 phase III study (Von Hoff, et al., 2013). On 21 November 2013, EMA's Committee for Medicinal Products for Human Use (CHMP) adopted a positive opinion recommending the change of the marketing authorization of Abraxane® in Europe to include "Abraxane in combination with gemcitabine is indicated for the first-line treatment of adult patients with metastatic adenocarcinoma of the pancreas".

2.6.1 Preclinical studies with *nab*-paclitaxel

A range of preclinical studies in the appropriate species have been completed with *Nab*-paclitaxel including single and repeat-dose toxicity studies, carcinogenicity evaluations, reproductive toxicity assessments, and mutagenicity and toxicity studies. A thorough discussion of these is included in the Investigator's Brochure (IB) (Abraxis BioScience, Celgene Corporation, 2013).

Preclinical studies comparing *nab*-paclitaxel to Taxol demonstrated lower toxicities, with a maximum tolerated dose (MTD) approximately 50% higher for *nab*-paclitaxel compared to Taxol. At equitoxic doses of paclitaxel, *nab*-paclitaxel was found to be markedly more efficacious in these animal models than Taxol.

2.6.2 Clinical studies with *nab*-paclitaxel - efficacy and safety data

Early-phase clinical studies with *nab*-paclitaxel confirmed the efficacy and lower toxicity of nab-paclitaxel versus solvent-based paclitaxel. The advantages of using nab-paclitaxel included the ability to dose at higher levels (MTD at 300 mg/m^2), elimination of premedication requirements, shorter infusion durations (30 min), and elimination of the need for specialized IV infusion supplies to accommodate the corrosive effect of the solvent vehicle).

Nab-paclitaxel's antitumour activity has been observed in patients with metastatic breast or lung cancers, melanomas and other solid tumours.

Following numerous phase II studies of nab-paclitaxel (monotherapy or combinations) in breast cancer, a pivotal, controlled, multicenter, randomized, phase III study of *nab*-paclitaxel 260 mg/m^2 every 3 weeks without premedication in 460 patients with metastatic breast cancer (Celgene sponsored protocol CA 0120-0) demonstrated a superior target lesion response rate of nab-paclitaxel compared to that of solvent-based paclitaxel (175 mg/m^2 IV q3w) with similar toxicity and formed the basis for current approved indications in breast cancer and ongoing studies in other solid tumours indications (Abraxis BioScience, Celgene Corporation, 2013, p. 20), (Gradishar, et al., 2005).

In non-small cell lung cancer, the randomized phase III study (Celgene sponsored protocol CA 031) comparing the efficacy and safety of albumin-bound paclitaxel plus carboplatin with solvent-based paclitaxel plus carboplatin demonstrated that the administration of *nab*-paclitaxel as first-line therapy in patients with advanced NSCLC was efficacious and resulted in a significantly improved overall response rate versus solvent based paclitaxel. Significantly less grade ≥ 3 neuropathy, neutropenia, arthralgia and myalgia occurred in the *nab*-paclitaxel Arm, and less thrombocytopenia and anemia occurred in the solvent-based paclitaxel Arm (Socinski, et al., 2012).

Two clinical trials with nab-paclitaxel in combination with gemcitabine have been performed in pancreatic cancer:

In the phase I/II Abraxis protocol CA040 (Von Hoff, et al., 2011), (Abraxis BioScience, Celgene Corporation, 2013, pp. 41,73), *nab*-paclitaxel in combination with gemcitabine was administered weekly. A total of 67 patients with advanced metastatic pancreatic cancer were treated with *nab*-paclitaxel at doses ranging from 100 to 150 mg/m^2.

The MTD was 1,000 mg/m^2 of gemcitabine plus 125 mg/m^2 of *nab*-paclitaxel once a week for 3 weeks, every 28 days. At the MTD, the response rate was 48%, with 12.2 median months of OS and 48% 1-year survival.

Dose-limiting toxicities were sepsis and neutropenia. Sixty three patients (94%) experienced at least one treatment-related adverse event (AE) and 35 (52%) patients experienced at least one treatment-emergent SAE. *Nab*-paclitaxel related SAEs occurred overall in 14 (21%) of the patients. The largest percentage of *nab*-paclitaxel related SAEs were hematologic (overall 9%).

With the exception of dehydration, fever, gastrointestinal obstruction, febrile neutropenia and lung infection, no treatment-emergent SAE categories had more than 2 events. Reported dose delays were mainly due to blood/bone marrow treatment related AEs (mostly neutropenia). There were 2 dose interruptions of *nab*-paclitaxel due to treatment related AEs

anemia and dehydration, and 4 instances of dose interruptions for gemcitabine. A total of 4 treatment-related AEs involving blood/bone marrow (neutropenia) resulted in dose reductions, and 6 treatment-related AEs resulted in dose discontinuation. There were 3 treatment-emergent AEs resulting in death (lung infection, systemic infection, and adult respiratory distress syndrome), but only systemic infection was considered treatment-related. Patients treated with *nab*-paclitaxel in combination with gemcitabine had levels of myelosuppression consistent with those expected following treatment with taxanes.

The conclusion of the phase I/II study was that the regimen of nab-paclitaxel plus gemcitabine has tolerable adverse effects with substantial antitumor activity, warranting the subsequent phase III evaluation in the international multicenter CA046 protocol (Von Hoff, et al., 2013). This phase III study tested the efficacy of the combination of nab-paclitaxel and gemcitabine versus gemcitabine alone in improving the overall survival in patients with adenocarcinoma of the pancreas.

A total of 861 patients were randomly assigned to *nab*-paclitaxel plus gemcitabine (431 patients) or gemcitabine (430). The median OS was 8.5 months in the combination Arm as compared with 6.7 months in the monotherapy Arm (HR for death, 0.72; P<0.001). The survival rate was 35% in the *nab*-paclitaxel–gemcitabine group versus 22% in the gemcitabine group at 1 year, and 9% versus 4% at 2 years. The median PFS was 5.5 months in the *nab*-paclitaxel–gemcitabine group, as compared with 3.7 months in the gemcitabine group (HR for disease progression or death 0.69; P<0.001); the response rate according to independent review was 23% versus 7% in the two groups (P<0.001).

The most common adverse events of grade 3 or higher were neutropenia (38% in the *nab*-paclitaxel–gemcitabine group vs. 27% in the gemcitabine group), fatigue (17% vs. 7%), and neuropathy (17% vs. 1%). Febrile neutropenia occurred in 3% versus 1% of the patients in the two groups. In the combination Arm, neuropathy of grade 3 or higher improved to grade 1 or lower in a median of 29 days.

The proportion of patients with serious adverse events was similar in the two treatment groups (50% with *nab*-paclitaxel plus gemcitabine and 43% with gemcitabine). Fatal events were reported for 4% of the patients in each treatment group. Sepsis (all grades) was reported more often in the *nab*-paclitaxel–gemcitabine group than in the gemcitabine group (5% vs. 2%), as was pneumonitis (4% vs. 1%).

The study concluded that in patients with metastatic pancreatic adenocarcinoma, nab-paclitaxel plus gemcitabine significantly improved overall survival, progression-free survival, and response rate, with increases of peripheral neuropathy and myelosuppression rates. The results warranted the FDA approval of the combination nab-paclitaxel plus gemcitabine in first line of advanced or metastatic pancreatic cancer in September 2013.

For known safety risks of *nab*-paclitaxel and gemcitabine also *see Sections 5.1.4. and 5.2.3 General safety information* respectively.

2.7 Risk assessment

The present study will involve standard of care and an investigational combination in some patients. The addition of *nab*-paclitaxel to gemcitabine has been shown to be safe with tolerable toxicity and with potentially further clinical benefit (Von Hoff, et al., 2013), (Von Hoff, et al., 2011).

As detailed above, the most significant adverse events related to the administration of the combination regimen were myelosuppression and neuropathy.

Three of 67 patients died during the phase I/II study, due to lung infection, systemic infection and adult respiratory distress syndrome. The event of sepsis was considered

treatment related. In the phase III study, there were 18 deaths (4%) due to adverse events in each Arm (from 18/421 patients in the combination Arm and 18/402 patients in gemcitabine Arm).

Any drug related toxicity will be considered as per known safety risks defined in *Sections 5.1.4. and 5.2.3 General safety information* of *nab*-paclitaxel and gemcitabine respectively, and the decision to continue treatment in case of toxicity will be performed after a careful risk assessment for each patient. Patients will be continuously monitored for expected and unexpected events. The risk of fatal outcomes of potentially life-threating events such as febrile neutropenia, sepsis or pneumonitis should be reduced by early diagnosis and treatment.

The clinical risk-benefit relationship for administering the study regimens is regarded as favourable in both Arms. The combination treatment will also be made available to patients on monotherapy after progression.

Tumour biopsies in consenting patients that cannot provide previously archived tumour tissue samples will be performed using core needles preferably during endoscopic ultrasound (EUS) where possible or percutaneous under ultrasound (or CT) control. The reported complication rate following pancreatic core biopsies using different guided techniques is between 0 and 3.3% (Paulsen, Nghiem, Negussie, Higgins, Caoilli, & Francis, 2006), (Brandt, Charboneau, Stephens, Welch, & Goeliner, 1993), (Zech, Helmberger, Wichmann, Holzknecht, Diebold, & Reiser, 2002). The risk of secondary bleeding after biopsy although present is rare. The risk of infection is small, since tissue sampling is carried out under sterile conditions. More likely, complications could occur when structures near biopsy target are entered with needle (i.e. pancreatitis or other organ perforations with secondary fistulas). Secondary tumour seeding on the needle pass is also mentioned in literature. Immediate adverse events due to biopsies are easily detectable and are always searched for at the end of the procedure. Patients will be observed at the hospital for several hours after the procedure is completed. The patient has no direct known benefit from the tumour biopsy procedures at short term. However, biopsies are considered important for further translational research investigations that might bring new knowledge on the molecular profile of the disease.

Risks of collecting blood samples are small and routine for laboratory testing and patient care. Additional samples required for the study will be taken at the same time as standard sampling to avoid supplementary visits and vein punctures.

All other procedures (e.g. imaging, physical exams, etc.) are standard of care in this patient population.

2.8 Study rationale

Pancreatic cancer remains one of the most lethal tumours. Gemcitabine is the only current treatment worldwide approved, however the overall benefit in terms of PFS and OS is small.

The combination regimen of *nab*-paclitaxel and gemcitabine administered in patients with locally advanced or metastatic pancreatic cancer in a first line setting showed improved efficacy with acceptable toxicity. The study design allows patients in standard treatment to receive the combination treatment at tumour progression.

The proposed study will explore the impact of treatment on the quality of life and compare the times to definitive deterioration of the quality of life scores using the validated EORTC QLQ-C30. Efficacy and safety secondary endpoints are to be reported in a descriptive manner.

Molecular studies will be performed on blood and tissue samples. Of special interest are questions as to:

- patient specific factors contribute to response and clinical outcome
- tumour markers as indicators of response
- molecular profile of the disease

On the basis of the preclinical and clinical data available to date, the selection of the study population and the conduct of the study are regarded as justifiable, with a positive risk-benefit balance for patients in both treatment Arms.

3 Objectives of the trial

3.1 Primary objective

To compare quality of life scores and times to definitive deterioration of the QOL scores in patients receiving *nab*-paclitaxel + gemcitabine versus gemcitabine alone using the EORTC QLQ-C30 questionnaire.

3.2 Secondary objectives

To evaluate in both treatment Arms:

- Safety and tolerability profile (NCI-CTCAE v. 4.0)
- Overall response and duration of response as assessed by imaging (RECIST 1.1) and tumour markers
- Disease control rates
- Progression free survival and overall survival
- Changes in serum CA 19-9 and CEA and composite index CA19-9xCEA
- Exploratory biomarker analyses by immunohistochemistry, proteomics, microarray and polymerase chain reaction (PCR) studies on tissue, blood and blood products and correlations with outcome.
- Exploratory hypoxia studies. *See Section 10. Exploratory translational research.*

For exact descriptions of the corresponding endpoints, refer to *Section 11. Statistics.*

4 Investigational plan

4.1 Overall study design and plan

This multicenter study is designed to compare quality of life scores in patients receiving *nab*-paclitaxel + gemcitabine versus gemcitabine alone using the EORTC QLQ-C30 questionnaire.

For this, two treatment Arms [a combination regimen *nab*-paclitaxel + gemcitabine (investigational Arm A) and a standard regimen gemcitabine in monotherapy (Arm B)] are foreseen as described *in Section 5. Treatments* below.

Eligible patients must present with previously untreated, unresectable, histologically or cytologically confirmed locally advanced or metastatic adenocarcinoma of the pancreas.

Patients who fulfill all inclusion criteria (*See Section 4.3.1. Inclusion criteria*) and none of the exclusion criteria *(see Section 4.3.2. Exclusion criteria*) and sign informed consent may start treatment under this study protocol.

Eligible patients will be randomized between Arms by an automated 1:1 block randomization. The patients will be stratified by center, performance status (0 and 1 vs. 2), location of the tumour (head of the pancreas vs. other) and stage (locally advanced vs. metastatic).

The study design, treatment and procedures are summarized in *Figure 1: Study overview* Clinical procedures and timepoints are described in *Section 6. Methodology and study procedures* and summarized in

Table 4: Summary of clinical procedures and timepoints (Arm A and Arm B respectively).

4.2 Selection of participating centers

Belgian centers with experience in clinical research are selected.

Complete lists of participating centers will be available at the time of submissions.

4.3 Selection of study population

Patients are considered eligible for this trial if they fulfill all of the inclusion criteria and none of the exclusion criteria below. Refer to

Table 4: Summary of clinical procedures and timepoints for timing of screening evaluations in Arm A and Arm B respectively.

4.3.1 Inclusion criteria

1. Written informed consent (+ optional for TR) must be given according to ICH/GCP and national/local regulations.
2. Patient is at least 18 years of age[3].
3. Unresectable locally advanced or metastatic pancreatic cancer.
4. Histologically or cytologically confirmed adenocarcinoma of the pancreas. Islet cell neoplasms or neuroendocrine tumors are excluded.
5. Evaluable or measurable disease, not in a previously irradiated area.
6. Life expectancy of at least 12 weeks.
7. WHO ECOG performance status ≤ 2
8. Adequate organ function.
9. Adequate bone marrow, hepatic and renal function:
    - Hemoglobin $\geq$ 8.0 g/dL, absolute neutrophil count $\geq$ 1.5 x 10^9/L, platelet count $\geq$ 100 x 10^9/L
    - ALAT, ASAT $\leq$ 2.5 x ULN, up to $\leq$ 5 x ULN in case of liver involvement
    - Total bilirubin $\leq$ 2 x ULN. No jaundice.
    - Serum creatinine $\leq$ 1.5 x ULN and /or calculated creatinine clearance $\geq$ 60 mL/min (calculated according to Cockcroft and Gault).

[3] Patients with pancreatic adenocarcinoma aged 75 years and older should be carefully assessed for their ability to tolerate nab-paclitaxel in combination with gemcitabine with special consideration to performance status, co-morbidities and increased risk of infections.

10. Acceptable coagulation determined on routine tests (e.g. prothrombin time,, partial thromboplastin time, INR, etc within +/- 15% of normal limits or as per clinical practice).
11. No clinically significant abnormalities in urinalysis.
12. Effective contraception for both male and female patients if applicable. Women of childbearing potential must have negative blood pregnancy test at screening visit.

4.3.2 Exclusion criteria

1. Prior chemotherapy, surgery or other investigational therapy for the treatment for metastatic disease. Adjuvant treatment with gemcitabine or 5-FU is allowed provided at least 6 months have elapsed since completion of the last dose.
2. Major surgery within 4 weeks of the start of the study.
3. Irradiation within 3 weeks prior to study entry.
4. Brain metastasis (known or suspected).
5. Serious medical risk factors involving any of the major organ systems, including high cardiovascular risk including coronary stenting or myocardial infarction in the last year and psychiatric disorders.
6. Known infection with HIV or active infection with hepatitis B or C.
7. History of connective tissue disorders (eg. lupus, scleroderma, arteritis nodosa, etc).
8. History of interstitial lung disease.
9. History of peripheral artery disease.
10. Previous (within 5 years) or concurrent malignancies at other sites with the exception of surgically cured or adequately treated carcinoma in-situ of the cervix and basal cell carcinoma of the skin.
11. Known allergy or any other adverse reaction to any of the drugs or to any related compound.
12. Use of oral anticoagulants that interfere with the metabolic path of *nab*-Paclitaxel (cytochrome P450 isoenzymes CYP2C8 and CYP3A4) such as warfarin (Coumadin), rivaroxaban (Xarelto), etc, and the impossibility to switch anticoagulation treatment to low molecular weight heparin.
13. Organ allografts requiring immunosuppressive therapy.
14. Pregnancy or breast-feeding.
15. Medical, social or psychological condition which, in the opinion of the investigator, would not permit the patient to complete the study or sign meaningful informed consent.

4.3.3 Additional eligibility criteria for cross-over

Arm B:

1. Progression of tumour in patients receiving gemcitabine alone

and

2. No significant gemcitabine related toxicity grade $\geq$ 2 or events requiring treatment discontinuation.

Patients assessed for cross-over must still comply with all the general inclusion/exclusion criteria above to be eligible for treatment with *nab*-Paclitaxel.

Clinical judgement on a case to case basis is to be employed.

4.4 Removal of subjects from the study or study treatment

Subjects are free to discontinue the study at any time without giving their reason(s).

Patients are discontinued from study treatment by the treating physician for the reasons detailed in *Section 5.3.3. Study treatment discontinuation criteria.*

4.5 Study termination

Study termination is at the discretion of the sponsor in any of the following events:

- Medical or ethical reasons affecting the continued performance of the study.
- Difficulties in the recruitment of patients.
- Occurrence of AEs unknown to date in respect of their nature, severity and duration, or, unexpected incidence/severity of known AEs.

Safety data from the study will be reviewed by the sponsor, Celgene and investigators on an ongoing basis in order to ensure that the continuation of the study is appropriate.

5 Treatments

Patients will be randomized to receive *nab*-paclitaxel + gemcitabine or gemcitabine alone.

5.1 *Nab*-paclitaxel

Nab-paclitaxel (Abraxane®) is provided by Celgene as study labelled medication.

The medication will be produced under Good Manufacturing Practice (GMP) conditions.

The instructions below are applicable for study labelled medication Abraxane®.

5.1.1 Handling, packaging and labelling

Celgene will perform the labelling and the final packaging of the study medication under GMP conditions. Labels and handling instructions will be available in local languages.

Study labels can be found in the current *Appendix 3: Nab-paclitaxel labels/packaging concept – example*. Details of drug request and shipping procedures can be found in the MOP and its appendices.

The study medication will be delivered by Celgene to the participating sites in conformity with current regulations.

Batch numbers will be given in the Certificates of Release (CoRs). From the documentation on the study drug, it shall be possible to retrace the composition and pharmaceutical quality according to the current GMP guidelines. Participating sites / pharmacists are to complete and return to Celgene the signed acknowledgements of receipts (AoRs) after each study medication delivery.

5.1.2 Storage, reconstitution and destruction

Storage:

The study drug must be carefully stored at the study site, safely and separately from other drugs. Unopened vials of *nab*-paclitaxel are stable until the date indicated on the vial when stored in the original cartons at a controlled room temperature (20 to 25°C, excursions permitted between 15 and 30°C).

It must be ensured at each study site that the study labelled medication is not used:

- After the expiry date, or
- After the retest date unless the study drug is reanalyzed and its release date extended.

The local pharmacist is responsible for storage and accountability of the study labelled medication.

Reconstitution:

- Aseptically reconstitute each vial by injecting 20 ml of 0.9% sodium chloride injection over a minimum 1 minute using the sterile syringe to direct the solution flow onto the inside wall of the vial.
- Do not inject the 0.9% sodium chloride solution directly into the lyophilized cake as this will result in foaming.
- Allow the vial to sit for a min of 5 minutes to ensure proper wetting of the lyophilized powder
- Gently invert the vial for at least 2 minutes until complete dissolution occurs. Avoid foaming.
- If foaming or clumping occurs, stand solution for at least 15 minutes until foam subsides

The reconstituted sample should be milky and homogenous, without visible particulates.

Reconstituted *nab*-paclitaxel is compatible with standard infusion systems (tubing and bags). It was determined that in rare instances proteinaceous strands could appear in the infusion bag. Abraxane should always be administered using an infusion set that includes a 15 µm filter. A 15 µm filter removes strands without changing the physical or chemical properties of the reconstituted product. More details regarding the acceptable filters and infusion sets are available in the MOP.

From the microbiological point of view, reconstituted samples should be used immediately. If not used immediately, samples must be protected from light. Vials can be kept refrigerated at 2° to 8°C for a maximum of 8 hours if necessary. The suspension for infusion when prepared as recommended in an infusion bag should be used immediately but may be stored at ambient temperature (approx. 25°C) and protected from light for up to 4 hours. Discard any unused portion of the vial or bags.

Destruction:

All unused prepared product or left over at the end of the study will be disposed locally using own pharmacy forms and logs. The product should not be discarded into the environment. All used materials should be recovered and incinerated under controlled conditions in compliance with local and national regulations.

Drug accountability will be closely monitored by the responsible monitor as per routine practice.

For more instructions on storage, handling and preparation *see* the current Investigator's Brochure. For more instructions on drug requests and return/destruction *see* the MOP.

5.1.3 Administration

The study drug may not be used for any purpose other than the study and for registered, consenting patients. The administration of study medication to patients who have not been enrolled into the study is not covered by the study insurance.

Nab-paclitaxel must be administered under the supervision of a physician experienced in the use of antineoplastic medicinal products. Close monitoring is required during the infusion

and for at least one hour after the end of the infusion. Availability of resuscitation equipment must be ensured.

Exact documentation of actual dose, date, start time and end time of *nab*-paclitaxel infusion in the e-CRF is mandatory.

The administration procedures and dosage for *nab*-paclitaxel are as follows:

- *Sequence: Nab*-paclitaxel will always be administered before gemcitabine.
- D*ose:* Per protocol dose is 125 mg/m^2. Each vial of the reconstituted formulation contains 5ml paclitaxel per ml. The actual dose in mg and volume of the drug to be infused are dependent upon the patient's body surface area (BSA): Total dose (mg) = Per protocol dose (mg/m^2)*BSA (m^2). The exact dosing volume in ml required for the patient is calculated using the formula: Dosing volume (ml) = Total dose (mg) / 5mg/ml. For dose adjustments in case of neutropenia, thrombocytopenia or adverse events *see Appendix 4: BSA nomogram and Section 5.3. Dose modifications and treatment alterations.*
- *Administration of nab-paclitaxel*: The appropriate amount of reconstituted *nab*-paclitaxel is injected into an empty sterile PVC or non-PVC type IV bag.

  The volume is administered over a period of 30 minutes. Sterile sodium chloride solution (0.9%) is used to flush the line at the end of infusion. A physician must be available during the infusion and observation period post-infusion and vital signs are to be checked for patient safety as required during chemotherapy treatment.

- *Schedule:* The infusions will be repeated for three weeks followed by a week of rest (4 week cycles). *Nab*-paclitaxel infusions should be planned every 7 days on the same day of the week if possible; deviations more than 2 days are not allowed.

- *Premedication* is not necessary for *nab*-paclitaxel, however premedication with standard anti-emetics is recommended for gemcitabine and is to be administered prior to the infusion of *nab*-paclitaxel.

Patients randomized to Arm A may receive *nab*-paclitaxel until progression of disease occurs.

Patients starting treatment on gemcitabine alone (Arm B) and progressed are allowed to cross-over to the combination Arm if still able to receive treatment. These patients will start receiving *nab*-paclitaxel at the same dose, administration and schedule as patients initially randomized to Arm A.

5.1.4 General safety information

Through October 2012, approximately 3690 patients have been exposed to nab-paclitaxel during completed or ongoing Celgene-sponsored trials (Abraxis BioScience, Celgene Corporation, 2013) p.126.

The most important safety risks are presented below as emerged from the nonclinical and clinical development program, systematic review of the literature and post-marketing safety surveillance for the product. The incidence and severity of some adverse events (e.g. neuropathy) might vary depending on the schedule of administration.

Myelosuppression. The most important myelosuppressive of *nab*-paclitaxel is neutropenia. In 1310 patients treated with *nab*-paclitaxel monotherapy anemia was reported for 76% of patients, neutropenia for 74%, lymphopenia for 50% and thrombocytopenia for 19% of patients. Grade 3 neutropenia was reported for 22% and grade 4 neutropenia for 7% of patients. Of the 765 patients that received *nab*-paclitaxel in combination studies,

neutropenia was reported in 54% of patients, anemia for 41%, thrombocytopenia for 42% and leukopenia for 21%. Grade 3 or higher treatment related neutropenia was reported for 43% of patients.

Sensory neuropathy. Of 1310 patients treated with *nab*-paclitaxel monotherapy, 58% experienced sensory neuropathy. Of the 765 patients that received *nab*-paclitaxel in combination studies, peripheral sensory neuropathy was reported for 29%, which of 6% were grade 3 or higher.

Hypersensitivity reaction. In monotherapy trials, a total of 8 (<1%) of 1310 patients treated with *nab*-paclitaxel have experienced treatment related hypersensitivity. In combination studies 5 of 765 (<1%) patients experienced drug hypersensitivity. None of the reactions were grade 3 or higher. In post marketing surveillance, rare events of severe hypersensitivity reactions, including very rare events of anaphylactic reactions with fatal outcome have been reported.

Interstitial pneumonitis. Interstitial pneumonitis has been observed in less than 1% of treated patients both in monotherapy and combination trials. However, the risk appears to be somewhat higher for the combination of *nab*-paclitaxel with gemcitabine (4% in the combination Arm of the study CA046 (Von Hoff, et al., 2013) with two fatalities). Previous familial, environmental or occupational exposure, any episodes or transient dyspnea, cough, fever or respiratory infections during treatment should be carefully evaluated.

Infection/sepsis. Of 1310 patients treated with *nab*-paclitaxel monotherapy, a total of 32% were reported to have experienced some type of infection. Most commonly reported were urinary tract infections (6%), upper respiratory tract infections (5%), nasopharyngitis (3%), sinusitis (3%), pneumonia (2%) and cellulitis (2%). In addition, febrile neutropenia has been reported in 2%, sepsis in 0.3% and neutropenic sepsis in 0.2% of these patients. The risk appears to be higher in patients with pancreatic cancer receiving *nab*-paclitaxel in combination with gemcitabine. In the study CA046 (Von Hoff, et al., 2013), 22/421 (5%) of patients in the combination Arm and 10/402 (2%) of patients in the gemcitabine monotherapy Arm were reported to have developed sepsis with 5 and 2 fatalities respectively. The presence of biliary stent at baseline and complications due to the disease (compression on the bile duct) have been identified as contributing factors. Sepsis occurred on both neutropenic and non-neutropenic patients.

Cystoid macular edema is caused by intra- and extracellular edema leading to the formation of cystic spaces in the outer plexiform layer. Major symptoms are related to visual acuity. Frequency is less than 1 in 1000 patients.

Cardiotoxicity. Non-serious cardiac events have been reported in monotherapy clinical trials, mainly tachycardia in 10/1310 (<1.0%) and palpitations in 3/1310 (<1%). In the combination studies the most frequent cardiac events were also tachycardia and arrhythmia in 1% of patients. None of the reported events were grade 3 or higher. Rare events of congestive heart failure and ventricular dysfunction have been observed among individuals receiving *nab*-paclitaxel. While cardiotoxicity unequivocally related to *nab*-paclitaxel has not been demonstrated, cardiac events are not uncommon in the indicated population especially those with underlying cardiac or pulmonary disease. Cardiac function should be monitored.

Hepatotoxicity. In monotherapy studies, hepatotoxicity has been reported in 14% in 1310 with the most frequent being ALAT and ASAT increased (4%), ALP increased (3%) and bilirubin increased (1%). In combination therapy studies ALAT increased in 9%, ASAT in 8%, APL in 3% and bilirubin in 3% of patients. For pancreatic carcinoma *nab*-paclitaxel is not recommended for patients with moderate or severe hepatic impairment.

Gastrointestinal events. In some studies appeared that nausea, vomiting and diarrhea appeared to be more common with *nab*-paclitaxel than with solvent based paclitaxel, probably due to the prophylactic effect of the antiemetic medication normally administered in patients receiving the solvent-based paclitaxel. Of the 765 patients who received *nab*-paclitaxel in the combination studies, nausea have been reported in 32% of patients, vomiting in 17 and diarrhea in 12%. Only about 1% were grade 3 and higher. Nausea, vomiting and diarrhea can be treated with commonly used anti-emetic or anti-diarrheic agents.

Myalgia and arthralgia. Myalgia has been reported in 14% and arthralgia in 17% of patients both in monotherapy and combination studies with a 2% grade 3 or higher. Symptoms typically occurred 3 days after the *nab*-paclitaxel administration and resolved within one week. Myalgia and arthralgia are typically low grade, self-limiting and manageable with non-steroidal anti-inflammatory agents and acetaminophen.

Cranial nerve palsies. Cases of cranial nerve paralysis, including facial palsy have been reported. If neuropathy involving a cranial nerve occur, dose modifications might be justified determined by the nature, location and extent of the affected cranial nerve and based on a careful risk-benefit assessment.

Infusion site reactions/extravasations. Injection site reactions during IV administration may lead to localized edema, pain, erythema and indurations; on occasion, extravasation can result in cellulitis.

Elderly population. For patients of 75 years and older, no benefit for the combination treatment of *nab*-paclitaxel and gemcitabine in comparison to gemcitabine monotherapy has been demonstrated. In the very elderly (≥75 years) who received *nab*-paclitaxel and gemcitabine, there was a higher incidence of serious adverse reactions and adverse reactions that led to treatment discontinuation including hematologic toxicities, peripheral neuropathy, decreased appetite and dehydration. Patients with pancreatic adenocarcinoma aged 75 years and older should be carefully assessed for their ability to tolerate *nab*-paclitaxel in combination with gemcitabine with special consideration to performance status, co-morbidities and increased risk of infections.

5.2 Gemcitabine

Gemcitabine is given in standard indication and regimen both to patients in Arm A (in combination) and to patients in Arm B (alone).

5.2.1 Handling

Investigators should treat patients with commercially available forms of gemcitabine and use the approved harmonized European Summary of Product Characteristics (SmPC) (www.ema.europa.eu, 2008) for complete prescription information, storage, preparation and handling, administration, safety issues (warnings, precautions), adverse reactions, dose modifications and omissions.

5.2.2 Administration

Investigators should follow the current SmPC and institutional procedures for the administration.
Exact documentation of actual dose and date of infusions in the CRF is mandatory.

- *Sequence:* Gemcitabine must be administered after the *nab*-paclitaxel infusion in Arm A.

- D*ose:* Per protocol dose: 1000 mg/m^2. The actual dose in mg and volume of the drug to be infused are dependent upon the patient's body surface area (BSA). S*ee Appendix 4: BSA nomogram.*
- *Preparation:* instructions for handling and preparation of gemcitabine for infusion are as per SmPC and institutional practices.
- *Administration of gemcitabine:* The infusion is administered over 30 minutes. Prolongation of the infusion time has been shown to increase toxicity. Sterile sodium chloride solution (0.9%) is used to flush the line before and after infusion. A physician must be available during the infusion and observation period post-infusion and vital signs are to be checked for patient safety as required during chemotherapy treatment.
- *Schedule:* For patients in Arm A, gemcitabine will be given in the same day and following *nab*-paclitaxel, i.e. once weekly for the 3 weeks followed by a week of rest then repeat (4 week cycles). For patients in Arm B, gemcitabine will be given in an initial sequence of seven weeks followed by a week of rest (first cycle is 8 weeks) then every week for three weeks followed by a week of rest (cycle 2 and subsequent cycles are of 4 weeks). Gemcitabine infusions should be planned every 7 days on the same day of the week if possible; deviations more than 2 days are not allowed.

- *Premedication* with standard anti-emetics is recommended prior to gemcitabine and is to be administered prior to the infusion of *nab*-paclitaxel for patients in Arm A and prior to the infusion of gemcitabine for patient in Arm B.

For dose modifications and/or delays for gemcitabine-associated toxicity *see* the SmPC and *Section 5.3. Dose modifications and treatment alterations* below).

Patients in Arm A will receive gemcitabine (+*nab*-paclitaxel) until disease progression or discontinuation for other reason.

Patients starting treatment on gemcitabine alone (Arm B) and progressed are allowed to cross-over to the combination Arm if still able to receive treatment. These patients will start receiving *nab*-paclitaxel at the same dose, administration and schedule as patients initially randomized to Arm A while continuing to receive gemcitabine at the previous doses.

5.2.3 General safety information

The frequency and severity of the adverse reactions are affected by the dose, infusion rate and intervals between doses. Dose-limiting adverse reactions are reductions in thrombocyte, leucocyte and granulocyte counts.

The most commonly reported adverse drug reactions associated with gemcitabine treatment include nausea with or without vomiting, raised liver transaminases (AST/ALT) and alkaline phosphatase, reported in approximately 60% of patients; proteinuria and haematuria reported in approximately 50% patients; dyspnea reported in 10-40% of patients (highest incidence in lung cancer patients); allergic skin rashes occur in approximately 25% of patients and are associated with itching in 10% of patients. Fatigue, if not associated with anaemia, usually resolves after the first cycle.

Myelosuppression manifested by neutropenia, thrombocytopenia, and anemia occurs with gemcitabine as a single agent and the risks are increased when combined with other drugs. In clinical trials, grade 3-4 neutropenia, anemia, and thrombocytopenia occurred in 25%, 8%, and 5%, respectively of patients receiving single-agent. The frequencies of grade 3-4 neutropenia, anemia, and thrombocytopenia varied from 48% to 71%, 8 to 28%, and 5 to 55%, respectively, in patients receiving gemcitabine in combination with another drug.

Pulmonary toxicity and respiratory failure. Pulmonary toxicity, including interstitial pneumonitis, pulmonary fibrosis, pulmonary edema, and adult respiratory distress syndrome (ARDS), has been reported. In some cases, these pulmonary events can lead to fatal respiratory failure despite discontinuation of therapy. The onset of pulmonary symptoms may occur up to 2 weeks after the last dose of gemcitabine.

Hemolytic uremic syndrome. Hemolytic uremic syndrome (HUS) to include fatalities from renal failure or the requirement for dialysis can occur in patients treated with gemcitabine. In clinical trials, HUS was reported in 6 of 2429 patients (0.25%). Most fatal cases of renal failure were due to HUS. Renal function should be carefully assessed prior to initiation of gemcitabine and periodically during treatment. Consider the diagnosis of HUS in patients who develops anemia with evidence of microangiopathic hemolysis, elevation of bilirubin or LDH, or reticulocytosis; severe thrombocytopenia; or evidence of renal failure (elevation of serum creatinine or BUN). Permanently discontinue gemcitabine in patients with HUS or severe renal impairment. Renal failure may not be reversible even with discontinuation of therapy. Renal failure may not be reversible even with discontinuation of therapy.

Hepatic toxicity. Drug-induced liver injury, including liver failure and death, has been reported in patients receiving gemcitabine alone or in combination with other potentially hepatotoxic drugs. Administration of Gemzar in patients with concurrent liver metastases or a pre-existing medical history or hepatitis, alcoholism, or liver cirrhosis can lead to exacerbation of the underlying hepatic insufficiency. Assess hepatic function prior to initiation of gemcitabine and periodically during treatment. Discontinue gemcitabine in patients that develop severe liver injury.

Exacerbation of radiation therapy toxicity. As per the summary of product characteristics, gemcitabine is not indicated for use in combination with radiation therapy. Life-threatening mucositis, especially esophagitis and pneumonitis occurred in trials in which gemcitabine was administered at a dose of 1000 mg/m^2 to patients with non-small cell lung cancer for up to 6 consecutive weeks concurrently with thoracic radiation given together or less than 7 days apart. Excessive toxicity has <u>not</u> been observed when gemcitabine is administered more than 7 days before or after radiation. Radiation recall has been reported in patients who receive gemcitabine after prior radiation. Temporary discontinue or delay gemcitabine in patients that need radiotherapy for symptom control not on target lesions, such as gemcitabine is administered at least 7 days apart from radiotherapy. No concurrent radiotherapy and gemcitabine is permitted.

Capillary leak syndrome Capillary leak syndrome (CLS) with severe consequences has been reported in patients receiving gemcitabine as a single agent or in combination with other chemotherapeutic agents. Discontinue gemcitabine if CLS develops during therapy.

Cardiovascular. Due to the risk of cardiac and/or vascular disorders with gemcitabine, particular caution must be exercised with patients presenting a history of cardiovascular events.

Elderly population (> 65 years). Gemcitabine has been well tolerated in patients over the age of 65. There is no evidence to suggest that dose adjustments, other than those already recommended for all patients, are necessary in the elderly.

Sodium. Gemcitabine 1000 mg contains 17.5 mg (< 1 mmol) sodium per vial. This should be taken into consideration by patients on a controlled sodium diet.

5.3 Dose modifications and treatment alterations

5.3.1 General criteria for dose modifications

Every effort will be made to administer the full doses of *nab*-paclitaxel and gemcitabine.

Decisions on dose modifications in accordance with the toxic effects observed will be made on the day of treatment. The doses are to be adjusted according to the highest degree of toxicity during the previous cycle/after the previous infusion. If a patient develops several different toxic effects and there are conflicting recommendations, the dose reduction required for the most severe toxic effect must be chosen.

Toxicity will be graded using the NCI-CTCAE. *See Appendix 2: NCI-CTCAE v.4.0.*

Dose modifications are permanent. Once a dose reduction has been made, this will be continued for all subsequent infusions (the dose cannot be re-escalated).

Only two dose modifications are permitted. If a toxic effect of the same degree occurs again after one dose modification, a second dose modification is allowed. If further toxicity occurs or the criteria for resuming treatment are not met, the patient must be withdrawn from treatment.

Arm A: If *nab*-paclitaxel is to be discontinued for other reason than progression, patients in Arm A could continue treatment with gemcitabine off study protocol, if appropriate. If gemcitabine is to be discontinued for other reason than progression, patients in Arm A could continue treatment with *nab*-paclitaxel alone, on study protocol, if appropriate. If progressive disease or both drugs have to be discontinued for other reason, patients will be taken off study.

Arm B: If gemcitabine is to be discontinued for other reason than progression, patients in Arm B will be taken off study. In case of progressive disease, patients in Arm B are allowed to cross-over to the combination Arm A.

The following guidelines apply to the combination Arm A only. They outline dose adjustments in response to different toxic effects and the criteria for restarting treatment. Modifications to the dosages are based on drug induced hematological and non-hematological toxicity during the previous cycle.

For patients on standard gemcitabine (Arm B), dose modifications are to be done in accordance to the reference document (SmPC) and routine practice.

Dose level reductions for the combination of *nab*-paclitaxel with gemcitabine administered in patients with adenocarcinoma of the pancreas, as referenced in ***Table 2*** and ***Table 3*** are provided in ***Table 1***.

Table 1: Dose level reductions for patients with adenocarcinoma of the pancreas

Dose level	***Nab*-paclitaxel mg/m^2** (% of initial dose)	**Gemcitabine mg/m^2** (% of initial dose)
Initial full dose	125	1000
1st dose reduction	100 (80%)	800 (80%)
2nd dose reduction	75 (60%)	600 (60%)
3rd dose reduction	Not allowed → Discontinue	500 (50%)

		or discontinue
If additional dose reduction required		Discontinue

Table 2: Recommended dose modifications for neutropenia and thrombocytopenia at start or within a cycle

Cycle / Day	**ANC (cells/mm^3)**		**Platelet (cells/m^3)**	***Nab*-paclitaxel / Gemcitabine**
Day 1	<1500	OR	<100000	Delay doses until recovery
Day 8	500 to <1000	OR	50000 to < 75000	Reduce 1 dose level from Day 1
	<500	OR	<50000	Withhold doses
Day 15: If Day 8 doses were given without modifications:				
	500 to <1000	OR	50000 to < 75000	Treat with Day 8 dose level and follow with WBC Growth Factors OR Reduce 1 dose level from Day 8 doses
	<500	OR	<50000	Withhold doses
Day 15: If Day 8 doses were reduced:				
	≥ 1000	AND	≥ 75000	Treat with Day 8 dose level
	500 to <1000	OR	50000 to < 75000	Treat with Day 8 dose levels and follow with WBC Growth Factors OR Reduce 1 dose level from Day 8 doses
	<500	OR	<50000	Withhold doses
Day 15: If Day 8 doses were withheld:				
	≥1000	OR	≥75000	Treat with Day 1 dose levels and follow with WBC Growth Factors OR Reduce 1 dose level from Day 1 doses
	500 to <1000	OR	50000 to < 75000	Reduce one dose level from Day1 doses and follow with WBC Growth Factors.
	<500	OR	<50000	Withhold doses

Abbreviations: ANC=Absolute Neutrophil Count; WBC=white blood cell

Table 3: Recommended dose modifications for other adverse drug reactions

Adverse drug reaction	***Nab*-paclitaxel (mg/m^2)**	**Gemcitabine (mg/m^2)**
Febrile neutropenia gr. 3 or 4	Withhold until fever resolves and ANC ≥ 1500; resume at next lower dose level	
Peripheral neuropathy gr. 3 or 4	Withhold until improves to ≤ gr. 1; resume at next lower dose level.	No dose reduction
Cutaneous toxicity gr. 2 or 3	Reduce to next lower dose level; discontinue treatment if toxicity persists.	
Gastrointestinal toxicity: gr. 3 mucositis or diarrhea	Withhold until improves to ≤ Grade 1; resume at next lower dose level.	

In line with standard clinical practice, a patient that develops severe hypersensitivity reaction to *nab*-paclitaxel should be immediately discontinued from treatment and not be re-challenged.

Upon a diagnosis of interstitial pneumonitis, *nab*-paclitaxel and gemcitabine should permanently be discontinued. After ruling out an infectious etiology, intravenous high-dose corticosteroid therapy should be instituted without delay with appropriate premedication, secondary pathogen coverage, immunomodulation and supportive ventilation.

Asymptomatic or clinically mild pulmonary embolism can be treated with low-molecular weight heparin without interruption of therapy. Moderate to severe pulmonary embolism will require permanent discontinuation of treatment.

Permanently discontinue gemcitabine for any of the following: unexplained dyspnea or other evidence of severe pulmonary toxicity, severe hepatic toxicity, hemolytic-uremic syndrome, capillary leak syndrome.

Careful monitoring for infection / sepsis signs and symptoms is recommended with early intervention as appropriate: use broad spectrum antibiotics such as ciprofloxacin or augmentin at the first occurrence of fever ≥38.5°C regardless of neutrophil counts. On their first visit, patients should be provided with enough ciprofloxacin (or the alternative antibiotic) for use at home, and they should be instructed to begin taking it when they first record a temperature of ≥38.5 °C (or if they feel they are developing a fever and a thermometer is not available). A full sepsis diagnostic work-up should be performed while continuing broad spectrum antibiotics. If cultures are positive, the antibiotic may or may not be changed, depending on the sensitivity profile of the isolated organism. Patients with persisting fever after 3 weeks, despite uninterrupted antibiotic treatment, will discontinue study treatment.

Colony stimulating factors may be given according to institutional guidelines for the treatment of neutropenic fever or infections associated with neutropenia and for the prevention of febrile neutropenia in patients with an ANC <500 cells/µL. Patients not experiencing resolution of neutropenia within 21 days, despite uninterrupted G-CSF (Granulocyte-Colony Stimulating Factor) treatment, will discontinue study treatment.

If grade 3 mucositis or diarrhea occurs, study drug should be withheld until resolution to ≤ grade 1, then reinstituted at the next lower dose level of both drugs. Patients who develop grade 4 mucositis or diarrhea should have treatment discontinued.

Study drug should only be administered if hepatic function is within the parameters established in the eligibility criteria. Hepatic toxicity from taxanes may occur but it is uncommon. Therefore, hepatic dysfunction that occurs while the patient is on study should

prompt an evaluation to determine the cause, including the possibility of progressive metastatic disease and hepatotoxicity from concurrent medications.

Preventive steps for cystoid macular edema are unknown. Secondary prevention is focused on early detection of visual symptoms discontinuation of treatment in affected patients. Cystoid macular edema is expected to resolve within a couple of weeks from treatment discontinuation.

If a patient develops an intercurrent illness (e.g., infection) that, in the opinion of the investigator, mandates the interruption of therapy, that intercurrent illness must resolve within a time frame such that no more than two consecutive infusions of *nab*-paclitaxel are withheld. After the interruption, treatment will resume at the last weekly dose before the interruption.

Temporary discontinue or delay gemcitabine in patients that need radiotherapy for symptom control not on target lesions, such as gemcitabine is administered at least 7 days apart from radiotherapy. No concurrent radiotherapy and gemcitabine is permitted. Radiotherapy aimed at main disease (target lesions) is not allowed.

If there are conflicting recommendations, the decision whether to restart treatment must be based on the most severe toxic effect observed.

If therapy must be withheld for a longer period of time than 2 consecutive infusions and a week of rest, the patient will be discontinued from the study treatment.

5.3.2 Rules for Dose Omissions and Modified Schedules

Arm A patients:

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 (i.e. 1-2-3-Rest, X-1-2-3-Rest, etc.).

Day 8 dose missed:

Cycle continues per protocol, with one dose not given (i.e., 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 (i.e. 1-2-3-Rest, 1-2-X, 1-2-3-Rest, etc.).

The maximum delay between a missed scheduled dose and the next one (whichever dose was missed) should not be longer than 21 days that is 2 infusions and a week of rest, except for peripheral neuropathy grade 3 or 4 where an additional delay of 2 extra infusions and a week of rest might be acceptable after discussion with the central investigator.

Arm B patients:

As per reference document (SmPC) and routine practice.

For more information on coding the infusion and cycle numbers in case of treatment delays *see* the MOP and its appendices.

5.3.3 Study treatment discontinuation criteria

Treatment with *nab*-paclitaxel, gemcitabine or both could be discontinued in case of:

- Disease progression[4] of patients in Arm A or cross-overs.
- Disease progression[4] of patients in Arm B that are not suitable for continuing treatment with *nab*-paclitaxel + gemcitabine.
- Unacceptable toxicity attributed to study therapy after appropriate dose adjustments *see Section 5.3.1.General criteria for dose modifications.*
- Occurrence of an exclusion criterion which is clinically relevant and affects the patient's safety, if discontinuation is considered necessary by the investigator.
- Withdrawal of consent, patient request or decision of the investigator.
- Intercurrent illness or treatment delays longer than the equivalent interval of two treatment administrations and a week of rest.
- Patient best interest e.g. initiation of other anticancer therapy, radiotherapy, surgery, or other intervention[5].
- Intake of non-permitted medication or procedure.
- Insufficient patient compliance (defined as missing more than two doses of *nab*-paclitaxel).
- Occurrence of pregnancy.
- Study closure

Arm A: If *nab*-paclitaxel is to be discontinued for other reason than progression, patients in Arm A could continue treatment with gemcitabine alone off study protocol, if appropriate. If gemcitabine is to be discontinued for other reason than progression, patients in Arm A could continue treatment with *nab*-paclitaxel alone on study protocol, if appropriate. If progressive disease or both drugs have to be discontinued for other reason, patients will be taken off study.

Arm B: If gemcitabine is to be discontinued for other reason than progression, patients in Arm B will be taken off study. In case of progressive disease, patients in Arm B are allowed to cross-over to the combination Arm A, if appropriate.

If there is a safety reason for the withdrawal, the patient will remain under the supervision of the investigator until the AEs have resolved.

If a patient has failed to attend scheduled assessments in the study, the investigator must determine the reasons and the circumstances as completely and accurately as possible.

In case of premature discontinuation of treatment by a subject, the investigations scheduled for the "End of Treatment" visit should be performed (specifically a CT- or MRI scan).

In any case, the e-CRF section entitled "End of Treatment" must be completed.

The quality of life questionnaire will be collected every four weeks from all living patients for a maximum of 12 months from treatment start regardless of the reason of discontinuation.

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[4] Appropriate imaging techniques should be used to document progression. If clinical progression occurs, a CT/MRI scan should be performed as soon as possible after cessation of treatment.

[5] If applicable, treatment could resume after recovery at previous treatment doses (if treatment interrupted for less than 21 days).

Survival status will be collected for all patients, at routine follow up visits if applicable or by telephone. Survival data will be documented in the CRF until the database lock and on simplified electronic forms for up to three years afterwards.

5.4 Prior and concomitant therapy

All chemotherapy treatment administered before inclusion in the study must be recorded, including start date and stop date of the treatment, doses, regimen, and dose reductions (including reasons), relapse information. Only treatment administered in adjuvant settings is allowed.

Concomitant medication or medication administered during the study (beginning at 3 weeks before treatment start) must be recorded. All pain and symptomatic medication that would influence quality of life must be listed in the CRF, frequency and doses specified.

Over the course of this trial, additional medications may be required to manage aspects of the disease, including side effects from trial treatments or disease progression. Supportive care, including but not limited to anti-emetic medications, may be administered at the discretion of the Investigator. Human albumin is the only excipient in the nab-paclitaxel; the formulation does not contain ethanol and does not require premedication with anti-histamines. However, standard premedication for gemcitabine is recommended.

Irradiation of target lesions is not allowed during the study. Radiotherapy for symptom control not on target lesions may be permitted at the condition that is administered at least 7 days apart from the administration of gemcitabine. No concurrent radiation and gemcitabine is permitted.

Administration of other chemotherapy, immunotherapy, or anti-tumor hormonal therapy during the study is not allowed.

The metabolism of paclitaxel is catalysed, in part, by cytochrome P450 isoenzymes CYP2C8 and CYP3A4. Therefore, caution should be exercised when administering nab-paclitaxel concomitantly with medicines known to inhibit CYP2C8 or CYP3A4 (e.g. ketoconazole, erythromycin, fluoxetine, imidazole antifungals, gemfibrozil, cimetidine, some anti-virals).

Similarly, the use of oral anticoagulants that interfere with the metabolic path of *nab*-Paclitaxel (cytochrome P450 isoenzymes CYP2C8 and CYP3A4) such as warfarin (Coumadin), rivaroxaban (Xarelto), etc, is not allowed during this study; low-molecular weight heparins (LMWH) should be used instead.

Erythropoietin or G-CSF may be administered at the discretion of the Investigator, consistent with institutional guidelines. Growth factors are not allowed in primary prophylaxis but may be used for management and secondary prophylaxis of hematological complications.

Ciprofloxacin (or the alternative antibiotic) should be distributed to patients with instructions to begin treatment if they experience a febrile episode. Administration of long-term prophylactic ciprofloxacin (or the alternative antibiotic) to prevent recurrences in patients already having experienced a first febrile episode (and managed as described in *Section 5.3.1*) will be at the discretion of the treating physician.

Administration of prophylactic antibiotics to otherwise uncomplicated patients with biliary stents will be at the discretion of the treating physicians. Biliary stents should be monitored closely to determine need for replacement.

For information regarding other drugs that may interact with either *nab*-paclitaxel or gemcitabine and affect their metabolism, pharmacokinetics, or excretion see the reference documents.

Yellow fever vaccine and other live attenuated vaccines are not recommended in patients treated with gemcitabine.

Additionally, any diagnostic, therapeutic, or surgical procedures performed during this study period should be recorded in the e-CRF, including the date, indication, description of the procedures, and any clinical findings.

5.5 Treatment compliance

Since study medication is administered in a hospital or in an outpatient setting, compliance can easily be supervised. The importance of adherence to the recommended treatments should be emphasized to the patient.

The medication will be administered either by the investigator or under his direct supervision.

Date and time of the start and end of infusion, the exact amounts of all drugs given at each infusion will be documented in the e-CRF.

As a routine precaution, patients enrolled in this study will be observed during the administration of treatments and for at least one hour after the end of the gemcitabine infusion or longer if clinically necessary in an area with resuscitation equipment and emergency agents (epinephrine, prednisolone equivalents, etc.) available. In the event that the treatment has to be interrupted during infusion, the clinical staff should make an estimate of the percentage of dose received by the patient and document it in the e-CRF. Any reason for non-compliance should also be documented. Insufficient compliance is defined as a patient missing more than two infusions of either *nab*-paclitaxel or gemcitabine without medical reason.

In the event of insufficient compliance, discontinuation of study treatment will be considered in mutual agreement between the investigator and the central PI on a case-by-case basis.

6 Methodology and study procedures

For a summary of procedures and timepoints for each Arm *see*

Table 4: Summary of clinical procedures and **timepoints**.

6.1 Screening

All patients seen in clinic and considered potentially eligible for the study will be recorded on the provided screening log (*See* MOP). In cases when, after completing the screening process, a patient is subsequently not enrolled in the study, the reason of non-enrolment should be mentioned in the screening log. This document will be kept by each site and presented at monitoring visits or upon request.

Screening procedures are:

- Verification of all inclusion and exclusion criteria.
- Tumour diagnosis / staging. If the patient is registered, existing imaging studies can be used as baseline evaluations if performed within 28 days from the first day of treatment.

- Medical history – relevant conditions and treatments. Current symptoms if applicable. Assessment of concomitant medication.
- History of adjuvant chemotherapy treatment(s), including duration and relapse information.
- Clinical examination/physical exam.
- Laboratory information:
    - Hematology: Erythrocytes, hemoglobin, hematocrit, white blood cell count, differential, and platelet count.
    - Chemistry: Glucose, total bilirubin, ALAT, ASAT, alkaline phosphatase, serum creatinine, total protein, sodium, potassium, magnesium (q8weeks), chloride, serum calcium, blood urea, and lactate dehydrogenase, CRP, routine coagulation tests.
    - Urine dipstick.

If the patient is registered, existing laboratory data can be used as baseline evaluation if performed within 2 weeks from the first day of treatment.

No clinical data will be recorded on screening failures in the e-CRF but the reason of non-eligibility must be documented in the screening log.

6.2 Informed consent

The informed consent form (s) (participation in the clinical trial, tissue retrieval or optional biopsy) must be signed by all eligible patients before undertaking any study related treatment, procedures or performing any data collection.

No biological materials for translational research can be collected before signature of the informed consent form.

See Section 13.3. Subject consent and the *Patient information and consent form* for details.

6.3 Randomization and allocation of patient number

All eligible patients that signed informed consent will be registered in the e-CRF. Separate consent signature for optional biopsies if applicable will also be recorded in the e-CRF.

Patients will be centrally and automatically randomized by the electronic CRF (for patient registration online *see* MOP).

A minimization technique [minimizing imbalance in the distributions of treatment numbers within the levels of each individual prognostic factor (Pocock & Simon, 1975)] will be used for random treatment allocation stratifying by the following factors:

- Center
- WHO ECOG performance status (0 and 1 versus 2)
- Location of tumour (head of the pancreas versus other location)
- Stage (locally advanced versus metastatic disease)

At registration, the electronic system will automatically assign a unique patient number in the format CC-PPP (C=center, P=patient).

Patients entering the study will retain this number throughout the study. The assigned unique patient number will not be reused.

6.4 Baseline

- Perform complete physical examination with WHO ECOG performance status and vital signs if not done during screening (within 2 weeks from start of treatment). Repeat WHO ECOG PS and vital signs prior to start of therapy. *See Appendix 5: WHO ECOG PS scale.*
- Repeat imaging studies if screening/eligibility scans were performed more than 28 days prior to the expected start of therapy.

  Disease evaluation: CT- or MRI-scan for baseline tumour assessment (chest, abdomen, pelvis). Date of diagnosis, histology, localization of tumour and TNM staging are required at registration. A chest X-Ray is not considered appropriate for the purpose of disease evaluation at baseline. However, if no lesion was observed in the thorax by CT or MRI during screening, at the subsequent visits a chest X-Ray could be used to evaluate the disease status. In these cases, any new suspected lesion on X-Ray will be confirmed by CT or MRI. NB. The same evaluation method of the target lesions should be consistently used throughout the study. For subsequent tumour evaluation timepoints in each Arm *see*

  Table 4: Summary of clinical procedures and **timepoints**.
- Cardiac examination: Electrocardiogram (ECG) performed at baseline for all patients (within 28 days prior to start of therapy). If a patient shows any sign of a cardiac event during the course of the study, a complete cardiac assessment should be performed.
- Laboratory examination. Repeat if not done within 2 weeks prior to treatment start. Blood counts at maximum 48 hours prior to the first infusion. NB. All clinical laboratory evaluations (hematology, chemistry, CA 19-9, CEA and pregnancy test) will be performed by the local laboratory of the investigational site complying with the principles of Good Clinical Practice (GCP) and local requirements. For subsequent safety and tumour evaluation timepoints in each Arm *see*
- *Table 4: Summary of clinical procedures and* **timepoints**.
- CA 19-9 and CEA within 2 weeks prior to treatment start.
- Perform pregnancy test on blood within 7 days prior to treatment start in women with childbearing potential, if applicable.
- Record demographic and medical baseline data (including baseline symptoms and concomitant medication). Record baseline laboratory values with local normal ranges.

6.5 Baseline blood and tissue samples for translational research

For the duration of the study, every effort should be made that blood collection for translational research is performed at the same time with sampling for clinical laboratory where applicable, so the numbers of vein punctures and visits are reduced (for example, routine hematology and biochemistry and TR samples may be collected the same day, 1 hour before infusion).

Prior to the first infusion on study the following materials are required for translational research:

- Blood samples for translational research (10 ml whole blood, 10 ml for plasma and 10 ml for serum).

- Previously archived tissue from the pancreatic tumour if available. Paraffin embedded blocks (preferred) or a minimum of 15 slides.

OR

- Tissue from pancreatic lesion collected by core needle biopsy (during EUS or percutaneous with ultrasound or CT guidance in consenting patients if archived tissue is not available. Biopsy is to be performed after signature of consent and before the first infusion.

See Section 10. Exploratory translational research and the MOP for details on collection, handling, storage and shipping.

6.6 Cycle 1

6.6.1 Infusion visit Day 1

- Have the patient complete the Quality of Life questionnaire. It is recommended the patient completes the forms in clinic, before any appointment or procedure. Enough time should be allowed prior to his/her appointment.
- Physical safety check (presence of any new symptoms) every week.
- BSA every week. *See Appendix 4: BSA nomogram.*
- WHO ECOG performance status every week.
- Blood sampling for routine hematology and chemistry testing (local labs): the results of these tests must be available before the administration of medication. Hematology testing (blood counts) must be performed within 48 hours prior to infusion for safety reasons. Chemistry is allowed within two weeks. If the lab results are not acceptable for treatment, infusions may be delayed for a maximum of two consecutive weeks.
- TR blood samples if not previously taken.
- Check of vital signs as needed for patient safety.

Medication:

  - Flush line. Premedication: standard anti-emetics
  - Arm A: Administration of nab-paclitaxel. Flush line with sodium chloride. Administration of gemcitabine. Flush line with sodium chloride.
  - Arm B: Administration of gemcitabine. Flush line.

  It is a prerequisite that a physician is present during this first administration of study medication. Means of resuscitation must be available.

- Recording of clinical and QOL data and adverse events: infusion related symptoms, concomitant medication (pain and symptomatic), premature infusion discontinuation, etc.

6.6.2 Infusion visits Day 8 and Day 15

- Physical safety check every week.
- BSA every week.
- WHO ECOG performance status every week
- Blood sampling for routine hematology and chemistry testing (local labs): the results of these tests must be available before the administration of medication. Hematology testing (blood counts) must be performed within 48 hours prior to infusion for safety

reasons. Chemistry is allowed within two weeks. If the lab results are not acceptable for treatment, infusions may be delayed for a maximum of two consecutive weeks. *(See Section 5.3. Dose modifications and treatment alterations.)*

- Check of vital signs as needed for patient safety.

Medication:

- Flush line. Premedication: standard anti-emetics
- Arm A: Administration of nab-paclitaxel. Flush line with sodium chloride. Administration of gemcitabine. Flush line with sodium chloride.
- Arm B: Administration of gemcitabine. Flush line.

- Recording of clinical data and adverse events: infusion related symptoms, concomitant medication (pain and symptomatic), premature infusion discontinuation, etc.

6.6.3 Infusion visit Day 22 – Arm B only

- Physical safety check every week.
- BSA every week.
- WHO ECOG performance status every week.
- Blood sampling for routine hematology and chemistry testing (local labs): the results of these tests must be available before the administration of medication. . Hematology testing (blood counts) must be performed within 48 hours prior to infusion for safety reasons. Chemistry is allowed within two weeks. If lab results are not acceptable for treatment, infusions may be delayed for a maximum of two consecutive weeks. *(See Section 5.3. Dose modifications and treatment alterations.)*
- Check of vital signs as needed for patient safety.

Medication:

- Flush line. Premedication: standard anti-emetics
- Arm B: Administration of gemcitabine. Flush line.

- Recording of clinical data and adverse events: infusion related symptoms, concomitant medication (pain and symptomatic), premature infusion discontinuation, etc.

Patients in Arm A have a week of rest.

6.6.4 Infusion visit Day 29 – Arm B only

- Have the patient complete the Quality of Life questionnaire. It is recommended the patient completes the form in clinic, before any appointment or procedure. Enough time should be allowed prior to his/her appointment.
- Physical exam every 4 weeks.
- BSA every week.
- WHO ECOG performance status every week.
- Blood sampling for routine hematology and chemistry testing (local labs): the results of these tests must be available before the administration of medication. Hematology testing (blood counts) must be performed within 48 hours prior to infusion for safety reasons. Chemistry is allowed within two weeks. If lab results are not acceptable for

treatment, infusions may be delayed for a maximum of two consecutive weeks. *(See Section 5.3. Dose modifications and treatment alterations.)*

- Check of vital signs as needed for patient safety.

Medication:

- Flush line. Premedication: standard anti-emetics
- Arm B: Administration of gemcitabine. Flush line.

- Recording of clinical and QOL data and adverse events: infusion related symptoms, concomitant medication (pain and symptomatic), premature infusion discontinuation, etc.

Patients in Arm A start Cycle 2. Repeat procedures as in Cycle 1. *See Section 6.7. Cycle >= 2.*

6.6.5 Infusion visits Day 36 and Day 43 – Arm B only

- Physical safety check every week.
- BSA every week.
- WHO ECOG performance status every week
- Blood sampling for routine hematology and chemistry testing (local labs): the results of these tests must be available before the administration of medication. . Hematology testing (blood counts) must be performed within 48 hours prior to infusion for safety reasons. Chemistry is allowed within two weeks. If the lab results are not acceptable for treatment, infusions may be delayed for a maximum of two consecutive weeks. *(See Section 5.3. Dose modifications and treatment alterations.)*
- Check of the vital signs as needed for patient safety.

Medication:

- Flush line. Premedication: standard anti-emetics
- Arm B: Administration of gemcitabine. Flush line.

- Recording of clinical data and adverse events: infusion related symptoms, concomitant medication, premature infusion discontinuation, etc.

Week 8 beginning at Day 50 is a week of rest.

6.7 Cycle >= 2

6.7.1 Infusion visit Day 1

- Have the patient complete the Quality of Life questionnaire. It is recommended the patient completes the form in clinic, before any appointment or procedure. Enough time should be allowed prior to his/her appointment. **The QOL questionnaire will be completed every four weeks (first visit of the cycle). If delays of treatment occur and the patient is present in clinic, the QOL questionnaire can be completed even if the treatment is not administered. If the patient is not present in clinic, the QOL questionnaire will be completed at the next visit without delay.**
- Physical exam every 4 weeks.
- BSA every week.

- WHO ECOG performance status every week.
- Blood sampling for routine hematology and chemistry testing (local labs): the results of these tests must be available before the administration of medication. Hematology testing (blood counts) must be performed within 48 hours prior to infusion for safety reasons. Chemistry is allowed within two weeks. If lab results are not acceptable for treatment, infusions may be delayed for a maximum of two consecutive weeks. (*See Section 5.3. Dose modifications and treatment alterations.)*
- Check of the vital signs as needed for patient safety.

Medication:

  - Flush line. Premedication: standard anti-emetics
  - Arm A: Administration of nab-paclitaxel. Flush line with sodium chloride. Administration of gemcitabine. Flush line with sodium chloride.
  - Arm B: Administration of gemcitabine. Flush line. From this week on, patients in arm B will receive gemcitabine every week for three (3) weeks, followed by a week of rest.

- Recording of clinical and QOL data and adverse events: infusion related symptoms, concomitant medication, premature infusion discontinuation, etc.

6.7.2 Infusion visit Day 8 and 15

- Physical safety check every week.
- BSA every week.
- WHO ECOG performance status every week.
- Blood sampling for routine hematology and chemistry testing (local labs): the results of these tests must be available before the administration of medication. Hematology testing (blood counts) must be performed within 48 hours prior to infusion for safety reasons. Chemistry is allowed within two weeks. If lab results are not acceptable for treatment, infusions may be delayed for a maximum of two consecutive weeks. *(See Section 5.3. Dose modifications and treatment alterations.)*
- Check of the vital signs as needed for patient safety.

Medication:

  - Flush line. Premedication: standard anti-emetics
  - Arm A: Administration of nab-paclitaxel. Flush line with sodium chloride. Administration of gemcitabine. Flush line with sodium chloride.
  - Arm B: Administration of gemcitabine. Flush line. From this week on, patients in arm B will receive gemcitabine every week for three (3) weeks, followed by a week of rest.

- Recording of clinical and QOL data and adverse events: infusion related symptoms, concomitant medication, premature infusion discontinuation, etc.

6.7.3 Infusion visit Day 22

After three administrations, a week of rest should be observed for patients in both Arms. Treatment should continue following the schema stated in *Figure 1: Study overview* until one of the reasons for discontinuation occurs. *See Section 5.3.3. Study treatment discontinuation criteria.*

For timing of procedures in each Arm during study *see*

Table 4: Summary of clinical procedures and **timepoints**.

6.8 Blood samples for translational research during treatment

Prior to the infusion at week 9 (after 2 cycles in Arm A and 1 cycle in Arm B) the following materials are required for translational research:

- Blood samples for translational research (10 ml for plasma and 10 ml for serum).

Details on procedures, handling, shipping and analyses are described in *Section 10. Exploratory translational research* and MOP.

6.9 Evaluations at each 8 weekly visit – tumour (response) evaluation visits

Additionally to the regular physical and laboratory evaluations, the following procedures will be performed every 8 weeks:

- Imaging: CT or MRI scan of abdomen and pelvis + chest CT or MRI (or chest X-ray if no lung lesion was detected at baseline. If a lesion is detected on chest X-ray it will be confirmed by CT or MRI scan). The same evaluation method should be consistently used throughout the study.
- CA 19-9 and CEA
- Magnesium

The tumour load/tumour response will be evaluated every 8 weeks for the duration on study, afterwards as per routine practice.

6.10 Cross-over – Arm B only

Patients in Arm B progressing on gemcitabine alone and still able to receive treatment (*See Section 4.3.3. Additional eligibility criteria for cross-over* are allowed to cross-over to the combination Arm and receive *nab*-paclitaxel at 125mg/m^2 and gemcitabine at the last received dose level while on Arm B.

First progression should be carefully documented.

An interruption of maximum one cycle (28 days) is allowed for the cross-over. Cycles will be of 4 weeks, as described for Arm A.

6.11 Blood samples for translational research at cross-over

At cross-over, the following materials are required for translational research:

- Blood samples for translational research (10 ml for plasma and 10 ml for serum).

Details on procedures, handling, shipping and analyses are described in *Section 10. Exploratory translational research* and MOP.

6.12 End of Treatment visit

Whatever the reason for treatment discontinuation is, a complete assessment of the disease status and safety has to be performed within 30 days from treatment cessation. ("End of Treatment" visit).

The End of Treatment (EOT) visit will be performed within one month from treatment stop and will always consist of the following examinations:

- Physical examination.
- Assessment of WHO ECOG PS.
- Check of vital signs.
- Blood sampling for hematology and chemistry.
- CA 19-9 and CEA.
- If applicable: CT- or MRI-scan if patient is withdrawn for other reason than progressive disease documented by imaging and/or if previous CT/MRI scan is older than 4 weeks. (Chest CT could be replaced by chest X-ray if absence of lung lesion at baseline).
- Tumour evaluation. Best response overall.
- Recording of adverse events / concomitant medication.
- Cardiac evaluation: ECG (to be done at the latest before any new cancer treatment).

Completion of the QOL questionnaire will continue every four weeks for a total of 12 months in surviving patients, regardless of treatment discontinuation.

6.13 Blood samples for translational research at the "End of Treatment" visit

Blood samples for translational research are required at End of treatment from all patients.

- Blood samples for translational research (10 ml for plasma and 10 ml for serum).

Details on procedures, handling, shipping and analyses are described in *Section 10. Exploratory translational research* and MOP.

Patients that crossed-over and already provided a blood sample at their first progression are required to provide another blood sample at the time of the second progression.

If the patient is taken off study for other reason than progression or death, blood samples are required at the time of the visit or within 30 days from treatment discontinuation, but before starting of any new treatment.

Details on procedures, handling, shipping and analyses are described in *Section 10. Exploratory translational research* and MOP.

6.14 Follow up

6.14.1 First Follow-Up visit

Completion of the QOL questionnaire will continue every 4 weeks for a maximum of 12 months in all surviving patients and may be posted to the patient with return envelopes to avoid supplementary visits if applicable.

The "First Follow Up" visit will be done at 6-8 weeks after the "End of treatment" visit.

The "First Follow Up" visit will consist of the following examinations:

- QOL questionnaire if applicable.
- Physical examination.
- Assessment of WHO ECOG PS.
- Check of vital signs.

- Blood sampling for hematology and chemistry
- If applicable (not done within the last 12 weeks, not-progressed patients, etc.): disease evaluation by imaging if a CT- or MRI-scan and CA19-9 and CEA.
- Recording of adverse events / concomitant medication.
- Survival status update if applicable.

6.14.2 Subsequent follow up visits

Follow up of the tumours of progressed patients is at the discretion of the investigator. If a patient was taken off study for other reasons than progression of disease, the disease status and date of progression should be regularly documented by imaging. The date of progression should be carefully documented in the e-CRF. Survival and progression data will be collected for a maximum of three years after the database lock. Survival status will be documented in the CRF until the database lock and on simplified electronic forms afterwards.

For patients undertaking subsequent anti-cancer treatments (e.g. radiotherapy, chemotherapy, surgery) the clinical data (date of start, duration, outcome, if applicable) should be collected and recorded in the e-CRF. See exceptions in censoring and definition of PFS in *Section 11.2. Secondary variables.*

Treatment related toxicity still present at the "First Follow Up" visit will be followed up until resolution or outcome is stable.

Survival status should be documented by the investigator after the "End of Treatment" Visit at each routine follow up visit. In case the patient is not scheduled for assessment visits survival status of all known living patients will be checked by telephone for a maximum of three years after the database lock. The date and reason of death should be clearly documented in the respective section of the e-CRF or in the simplified FU forms provided after the database lock.

The central electronic database will be hosted and thus accessible for 9 months after the "First Follow Up" visit of the last patient on study. In this time interval, clean up/queries of data must be finalized. After the database lock, the follow up and survival data will be completed and locally stored at each site (in provided electronic password protected forms). Summary reports to the sponsor will be required every six months for a maximum of three years after the database lock. Data identified by patient number will be sent to U.Z. Leuven or its assigned representative.

Table 4: Summary of clinical procedures and timepoints

ARM A

	D-28 to D1	RANDOMIZATION[11]	D-14 to D1	Treatment period									End of thx	FIRST FOLLOW UP VISIT[15]	FU
				C1D1	C1D8	C1D15	C1D22	C2D1	C2D8	C2D15	C2D22	Continuing thx			
Screening[1]	X														
Informed consent (main+optional for biopsy[2])	X														
Demographic data	X														
Eligibility	X														
Medical history/sy and thx	X														
Physical exam	X		X[3]					X				X (Q4wks)	X		X (routine)
QOL questionnaire[4]				X				X				X (Q4wks)	X		X (q4wks)
Tumour assessment[5]															
CT/MRI of abdomen and pelvis	X										X	X (Q8wks)	X (Q8wks)		X (routine)
Chest X-Ray or CT/MRI	X										X	X (Q8wks)	X (Q8wks)		X (routine)
CA19-9 and CEA	X		X[6]								X	X (Q8wks)	X (Q8wks)		X (routine)
WHO PS	X		X	X	X	X	-	X	X	X	-	X (3xq4wks)	X		X (routine)
Cardiac assessment (ECG)[7]	X												X		
Clinical lab[8]	X		X	X[9]	X	X	-	X	X	X	-	X (3xq4wks)	X		X (routine)
Magnesium[8]	X		X								X	X (Q8wks)	X		X (routine)
Pregnancy test[10]			F												
Premedication antiemetics[12]				X	X	X	-	X	X	X	-	X (3xq4wks)			
Nab-paclitaxel				X	X	X	-	X	X	X	-	X (3xq4wks)			
Gemcitabine				X	X	X	-	X	X	X	-	X (3xq4wks)			
Blood samples for TR[13]			X									X	X		
Archived tissue / biopsy for TR[14]			X												
Toxicity and AE/ safety check			X	X	X	X	X	X	X	X	X	X (cont)	X		X[16]
Concomitant medication	X		X	X	X	X	X	X	X	X	X	X (cont)	X		X
Subsequent anti-cancer thx															X
Survival status				X	X	X	X	X	X	X	X	X (cont)	X		X (cont)[17]

Notes:

1 All screened patients to be recorded in the screening log. Reason for no registration to be documented, if applicable. Screening failures are not recorded in the CRF.
2 Biopsies remain optional in patients for whom previously archived tumour samples are not available. An additional signature is required from patients consenting to biopsies.
3 Physical exam to be repeated before infusion if done more than 2 weeks before start of treatment.
4 The QOL questionnaire (EORTC QLQ-C30) is applied at baseline and then every 4 weeks for up to 12 months in surviving patients.
5 The assessment of tumour, response and disease status by imaging, CA19-9 and CEA will be done every 8 weeks.
6 Repeat CA19-9 and CEA if done more than 2 weeks before start of treatment.
7 Cardiac assessment by ECG at baseline and end of study. In the event of cardiac emergent symptoms, it will be performed at any time.
8 Clinical laboratory for safety within 2 weeks prior to first infusion.
Hematology (5 ml): Erythrocytes count, hemoglobin, hematocrit, white blood cell count, differential and platelet count. Blood cell counts should be monitored weekly during therapy, always within 48 hours prior to the infusion.
Clinical Chemistry (10 ml): Glucose, total bilirubin, ALAT, ASAT, alkaline phosphatase, serum creatinine, total protein, sodium, potassium, magnesium (q8weeks), chloride, serum calcium, blood urea and lactate dehydrogenase (LDH), CRP. Follow current practice, at least every two weeks.
Urine dipstick: at baseline and when clinically indicated.
9 Repeat blood cell counts if not done within 48 hrs from infusion.
10 Pregnancy test on blood sample for female patients (F) able to become pregnant at max 7 days prior to treatment start.
11 Randomization will be done 1:1 by the automated system. Registration online at https://www.qolinpac.net. Unique study identifier will be automatically assigned at the time of randomization.
12 Premedication with standard anti-emetics as per current practice is recommended prior to each infusion of gemcitabine. For patients in Arm A premedication is administered prior to the infusion of *nab*-paclitaxel.
13 Blood samples for TR: Whole blood, plasma serum at baseline. Plasma, serum at week 9 and progression. If reason for discontinuation is other than progression, the last sample is required at the time of the End of treatment visit or within 30 days from discontinuation, but before starting of any new treatment.
14 Retrieval of previously archived tissue (block or min 15 slides) or biopsy during EUS or percutaneous with ultrasound or CT control in consenting patients that cannot provide archived tumour samples.
15 The “First Follow Up” visit will be performed at 6-8 weeks after the end of treatment visit. Afterwards, the FU visits are routine practice. For un-progressed patients discontinued for other reasons, date of progression should be documented.
16 Until resolution of residual toxicity or documented outcome.
17 Updated reports every 6 months for a maximum of 3 years after the database lock.

Table 4: Summary of clinical procedures and timepoints

ARM B

	D-28 to D1	RANDOMIZATION[11]	D-14 to D1	Treatment period													End of thx	FIRST FOLLOW UP VISIT[16]	FU
				C1D1	C1D8	C1D15	C1D22	C1D29	C1D36	C1D43	C1D50	C2D1	C2D8	C2D15	C2D22	Continuing thx	Cross-over		
Screening[1]	X																		
Informed consent (main+optional for biopsy[2])	X																		
Demographic data	X																		
Eligibility	X																		
Medical history/sy and thx	X																		
Physical exam	X		X[3]					X				X				X (Q4wks)		X	X (routine)
QOL questionnaire[4]				X				X				X				X (Q4wks)		X	X (q4wks)
Tumour assessment[5]																			
CT/MRI of abdomen and pelvis	X										X					X (Q8wks)		X (Q8wks)	X (routine)
Chest X-Ray or CT/MRI	X										X					X (Q8wks)		X (Q8wks)	X (routine)
CA19-9 and CEA	X		X[6]								X					X (Q8wks)		X (Q8wks)	X (routine)
WHO PS	X		X	X	X	X	X	X	X	X	-	X	X	X	-	X(3xq4wks)		X	X (routine)
Cardiac assessment (ECG)[7]	X																	X	
Clinical lab[8]	X		X	X[9]	X	X	X	X	X	X	-	X	X	X	-	X (3xq4wks)		X	X (routine)
Magnesium[8]	X		X									X				X (Q8wks)		X	X (routine)
Pregnancy test[10]			F																
Premedication anti-emetics[12]				X	X	X	X	X	X	X	-	X	X	X	-	X (3xq4wks)	X (3xq4wks)		
Nab-paclitaxel				-	-	-	-	-	-	-	-	-	-	-	-	-	X[13] (3xq4wks)		
Gemcitabine				X	X	X	X	X	X	X	-	X	X	X	-	X (3xq4wks)	X (3xq4wks)		
Blood samples for TR[14]			X									X					X	X	
Archived tissue / biopsy for TR[15]			X																
Toxicity and AE/ safety check			X	X	X	X	X	X	X	X	X	X	X	X	X	X (cont)	X	X	X[17]
Concomitant medication	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X (cont)	X	X	X
Subsequent anti-cancer thx																			X
Survival status				X	X	X	X	X	X	X	X	X	X	X	X	X (cont)	X	X	X (cont)[18]

Notes:

1 All screened patients to be recorded in the screening log. Reason for no registration to be documented, if applicable. Screening failures are not recorded in the CRF.
2 Biopsies remain optional in patients for whom previously archived tumour samples are not available. An additional signature is required from patients consenting to biopsies.
3 Physical exam to be repeated before infusion if done more than 2 weeks before start of treatment.
4 The QOL questionnaire (EORTC QLQ-C30) is applied at baseline and then every 4 weeks for up to 12 months in surviving patients.
5 The assessment of tumour, response and disease status by imaging, CA19-9 and CEA will be done every 8 weeks.
6 Repeat CA19-9 and CEA if done more than 2 weeks before start of treatment.
7 Cardiac assessment by ECG at baseline and end of study. In the event of cardiac emergent symptoms, it will be performed at any time.
8. Clinical laboratory for safety within 2 weeks prior to first infusion.
   Hematology (5 ml): Erythrocytes count, hemoglobin, hematocrit, white blood cell count, differential and platelet count. Blood cell counts should be monitored weekly during therapy always within 48 hours prior to the infusion.
   Clinical Chemistry (10 ml): Glucose,total bilirubin, ALAT, ASAT, alkaline phosphatase, serum creatinine, total protein, sodium, potassium, magnesium (q8weeks), chloride, serum calcium, blood urea and lactate dehydrogenase (LDH), CRP, routine coagulation tests. Follow current practice, at least every two weeks.
   Urine dipstick: at baseline and when clinically indicated.
9 Repeat if not done within 48 hrs from infusion.
10 Pregnancy test on blood sample for female patients (F) able to become pregnant at max 7 days prior to treatment start.
11 Randomization will be done 1:1 by the automated system. Registration online at https://www.qolinpac.net. Unique study identifier will be automatically assigned at the time of randomization.
12 Premedication with standard anti-emetics as per current practice is recommended prior to each infusion of gemcitabine. For patients in Arm A premedication is administered prior to the infusion of *nab*-paclitaxel.
13 For patients eligible for cross-over
14 Blood samples for TR: Whole blood, plasma serum at baseline. Plasma, serum at week 9, cross-over and 2nd progression. If reason for discontinuation is other than progression, last sample is required at the time of the End of treatment visit or within 30 days from discontinuation, but before starting of any new treatment.
15 Retrieval of previously archived tissue (block or min 15 slides) or biopsy during EUS or percutaneous with ultrasound or CT control in consenting patients that cannot provide archived tumour samples.
16 The “First Follow Up” visit will be performed at 6-8 weeks after the end of treatment visit. Afterwards, the FU visits are routine practice. For un-progressed patients discontinued for other reasons, date of progression should be documented.
17 Until resolution of residual toxicity or documented outcome.
18 Updated reports every 6 months for a maximum of 3 years after the database lock.

6.15 Subsequent anti-cancer treatments

For patients taken off study for progressive disease, toxicity or other reasons, further management will remain at the discretion of the investigator. The start date and type of the any new treatment should always be documented in the e-CRF in the FU forms.

Patients discontinuing study treatment for other reasons than progression and undertaking a different anti-cancer treatment will be censored for progression at the date of starting the new anti-cancer treatment.

Data regarding any procedure determining interruption of treatment will be recorded in the e-CRF. Also, the date of subsequent progression should be updated in the e-CRF or reported as instructed in the FU procedures, *see Section 6.14. Follow up.*

7 Assessment of quality of life

The EORTC quality of life questionnaire QLQ-C30 (Aaronson, et al., 1993) is an integrated system for assessing the health related quality of life (QOL) of cancer patients. To date, more than 2200 studies using the QLQ-C30 have been registered.

This questionnaire was designed to be cancer specific, multidimensional in structure, appropriate for self-administration (i.e. brief and easy to complete) and applicable across a range of cultural settings.

The core questionnaire is the product of more than a decade of collaborative research. Several versions have been improved and further developed over time.

A supplementary module specifically for patients with pancreatic cancer is now being developed but it will not be used for the purpose of this study.

7.1 Structure of the questionnaire

The current version 3.0 incorporates a total of 30 items/questions within five functional scales (physical, role, cognitive, emotional, and social), three symptom scales (fatigue, pain, and nausea and vomiting), a global health status / QOL scale, 6 single items assessing additional common symptoms (dyspnea, loss of appetite, insomnia, constipation and diarrhea) and perceived financial impact of the disease as presented in *Table 5*.

Table 5: Structure of the QLQ-C30 version 3.0

	Scale	Number of items	Item numbers
Global health status / QOL scale			
Global health status / QOL	QL2	2	29, 30
Functional scales			
Physical scale	PF2	5	1 to 5
Role functioning	RF2	2	6,7
Emotional functioning	EF	4	21 to 24
Cognitive functioning	CF	2	20,25
Social functioning	SF	2	26,27
Symptom scales/single items			
Fatigue	FA	3	10,12,18

Nausea and vomiting	NV	2	14,15
Pain	PA	2	9,19
Dyspnea	DY	1	8
Insomnia	SL	1	11
Appetite loss	AP	1	13
Constipation	CO	1	16
Diarrhea	DI	1	17
Financial difficulties	FI	1	28

7.2 Completion of the questionnaire

The EORTC QLQ-C30 will be used in patient's first language, *see Appendix 1: EORTC QLQ-C30 quality of life questionnaire – Master document in English*. Dutch and French validated translations are available and provided by EORTC, submitted with the patient information sheet and consent form.

QOL questionnaires are to be completed by all patients at baseline and every four weeks afterwards. During the treatment period the questionnaires are filled in the clinic, prior to the infusion, before interaction with study staff or physician. If delays of treatment occur and the patient is present in clinic, the QOL questionnaire can be completed even if the treatment is not administered. If the patient is not present in clinic, the QOL questionnaire will be completed at the next visit without delay.

During the follow up period the questionnaires should also be completed every four weeks up to a maximum of 12 months in surviving patients and may be posted to the patient with return envelopes to avoid supplementary visits if applicable.

Before handing the questionnaire to the patient, the study nurse, coordinator or physician must complete the patient study number on the form.

Patients should be instructed to fill in their initials, birth date and date of completion and respond to all questions, by circling the appropriate number corresponding to the answer of choice. There are two types of questions, type 1 to rate items from "Not at all" to "Very much" on a scale from 1 to 4 and type 2 to rate health and quality of life on a scale from 1 to 7.

7.2.1 Missing forms

QOL assessments are likely to be missed because of the negative events experienced by patients, such as treatment toxicities, discontinuation due to disease progression, rapid deterioration, death. The information is to be provided by patient self-report at a particular point in time and cannot be retrieved at a later date from medical charts.

The QOL main endpoint of this trial depends on the quality and completeness of data provided by the QOL questionnaires.

Adequate infrastructure, trained personnel, sufficient printed materials and time for completion must be allocated to carry out the QOL assessments at the indicated timepoints.

Patients should be instructed every time to answer all questions.

It is useful to document and report the extent of and reasons for missing data e.g. administrative failure, patient refusal, patient too ill, visit not done, etc. The reasons why

questionnaires have not been completed may provide useful information to take into account at the time of analysis.

Always complete the reason for missing questionnaires in the provided comment boxes in the CRF.

7.3 QOL data handling

Data recording

The study nurse or physician must ensure that the questionnaire has been properly completed and handed by the patient at each required timepoint. At receipt, the nurse must quickly check the completeness of the questionnaire.

The study nurse must transcribe the exact answers provided by the patient on the paper form in the electronic CRF. If a questionnaire has not been completed at a certain timepoint, the reason for non-completion is to be specified in the CRF. If answers are missing to one or more questions, the reasons, if known, should also be mentioned in the corresponding form in the CRF.

Data monitoring and quality assurance

As the QOL patient self-reported scores are the main basis for the primary endpoint of the study, 100% of the data recorded in the CRF will be source data verified by monitors. Paper forms should be properly filed in order in patient files.

8 Assessment of efficacy

8.1 Disease (tumour) assessments

Only patients with measurable or evaluable pancreatic disease at baseline as defined by the RECIST criteria (v. 1.1) (Eisenhauer, et al., 2009) may be enrolled in this study.

Evaluation of lesions should be based on images obtained by either CT or MRI scan (if CT is contraindicated). The same method of assessment and the same technique should be used to characterize the disease at baseline and during the study.

Baseline evaluations should be performed as close as possible to the treatment start (maximum 28 days before start of study treatment). The number of organs in which metastatic disease has been confirmed should be defined.

If CT/MRI of chest is negative at baseline then the patient may be followed with chest X-rays. Once a lesion is detected by chest X-ray it will be confirmed by CT or MRI scan.

Evaluation of lesions should be performed every 8 weeks during treatment, at the “End of Treatment” visit if not already done within 4 weeks and at the “First Follow Up” visit. In case the discontinuation of treatment is not related to progression documented by imaging, a CT-scan or MRI will be performed at the End of Treatment visit and then as per routine practice. Date of progression should be documented in the CRF.

If treatment discontinuation was based on clinical judgement (i.e. clinical progression) tumour evaluation should be done as soon as possible after the treatment stop.

CA19-9 and CEA changes will be assessed by ELISA.

Patient clinical condition will be evaluated with periodic physical examinations and scoring of performance status. The correlation between objective tumour response change in CA19-9, CEA and overall survival will be assessed at the end of the study. Increases in CA19-9 or CEA levels should not be used as evidence for progressive disease or for removing patients from study.

8.2 Criteria for target and non-target lesions (RECIST)

To assess whether there is progression of disease, the tumour burden at baseline will be calculated and used for comparison with subsequent measurements. At baseline tumour lesions will be categorized as follows:

- Measurable: The lesion has clear borders and can be accurately measured in at least one dimension with longest diameter (LD) $\geq$10 mm with spiral CT scan (CT slice thickness is 5 mm or less) and 20 mm by chest X-Ray. Malignant lymph nodes $\geq$ 15 mm in short axis with spiral CT scan (CT slice thickness is 5 mm or less).

- Non-measurable: all other lesions including small lesions (LD < 10 mm with spiral CT scan or pathological lymph nodes $\geq$ 10 mm to <15 mm short axis) and truly non-measurable lesions. Lesions considered truly non-measurable include the following: leptomeningeal disease, ascites, pleural/pericardial effusion, inflammatory breast disease, lymphangitic involvement of skin or lung, abdominal masses/abdominal organomegaly identified by clinical exam that are not measurable by reproducible imaging techniques, bone lesions and cystic lesions Additionally, a tumour that is located in a previously irradiated area should not be considered measurable. Superficial and palpable lesions will be considered as non-measurable lesions for the purpose of this study.

8.2.1 Target lesions

- When more than one measurable lesion is present at baseline, all lesions up to a maximum of five lesions total and a maximum 2 lesions per organ, representative of all involved organs, should be identified as target lesions and will be measured at baseline.
- Target lesions should be selected on the basis of their size (lesions with the longest diameters), their suitability for accurate repetitive measurements by imaging techniques, and how representative they are for the patient's tumour burden.
- The same lesions should be evaluated at each measurement timepoint. The exact reference/location on CT slices should be recorded as additional identification of target lesion.
- Target lesions will be measured in one dimension (longest diameter). In addition to each measurement, the sum of all LDs of all target lesions will be calculated at each time point.
- The baseline sum of LDs will be used as the reference by which to characterize the objective tumour response while progression will be diagnosed taking the smallest sum of longest diameters achieved (either at baseline or during study treatment) as reference.

8.2.2 Non-target lesions

- All other lesions (or sites of disease) should be identified as non- target lesions and also be documented. Measurements of these lesions are not required but nevertheless the presence, absence or unequivocal progression or regression of these lesions should be noted throughout the study.

8.3 Response criteria per timepoint

Overall response will be defined based on the assessments for target and non-target lesions as well as considering the occurrence of new lesions. RECIST definitions are as described in *Table 6* and *Table 7*:

Table 6: Response of target lesions

Complete response (CR)	Disappearance of all target lesions. No pathological lymph nodes (<10 mm in short axis). No new lesions.
Partial response (PR)	A 30% or more decrease in the sum of LD of target lesions, taking as reference the baseline sum of LDs, with no evidence of PD in non-target lesions or occurrence of new lesions.
Stable disease (SD)	Neither sufficient decrease to qualify for PR nor sufficient increase to qualify for PD taking as reference the smallest sum of LDs achieved throughout the study. No new lesions.
Progressive disease (PD)	A 20% or more increase in the sum of LDs of target lesions, compared to the smallest sum of LDs recorded for the study period (nadir sum of LDs). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. The appearance of any new lesion is automatically considered PD.

Table 7: Response of non-target lesions

Complete response (CR)	Disappearance of all non-target lesions and normalization of tumour marker level. No pathological lymph nodes (<10 mm in short axis). No new lesions.
No change (NC)	No significant change in non-target lesions to qualify for either CR or PD and/or maintenance of the tumour marker level above the normal limits. No new lesions.
Progressive disease (PD)	Appearance of one or more new lesions, and/or unequivocal progression of existing non-target lesions (worsening or new effusions or ascites in case of stable or responding target lesions will not be considered radiologic progression)*

*Although a clear isolated progression of "non-target" lesions only is exceptional, in such circumstances, the opinion of the treating physician should prevail.

In certain 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 (i.e. biopsy) before confirming the complete response status.

To assign a status of partial response, changes in tumour measurements must be confirmed to show 30% decrease in the sum of LDs compared to baseline, no less than 8 weeks after first dose of treatment.

In case of stable disease, measurements must have met the SD criteria at least once, no less than 8 weeks after first dose of treatment, otherwise the response will be not evaluable (NE). If the duration of SD is less than 8 weeks, the best response will be disease progression

If progressive disease was assigned to a timepoint due to unavailable scans, and is followed chronologically by a timepoint with no evidence of progression, then the timepoint with unavailable scans will be overruled in determination of the best overall response. Otherwise the response remains as PD.

When no imaging/measurement is done at all (or some lesions were not measured) at a particular timepoint, the patient is not evaluable (NE) at that timepoint.

Overall response per time point will be derived from the tumour response assessments obtained for target lesions and non-target lesions considering whether new lesions appeared at the respective time point or not. Overall responses for all possible combinations of tumour responses are provided in *Table 8*. Assessments of overall response should be provided and recorded in the CRF for each individual visit when tumour (response) evaluation is scheduled.

No confirmation of response is planned for this trial (Eisenhauer, et al., 2009).

Table 8: Overall response per timepoint assessment

Target lesions	Non-Target lesions	New Lesions	Overall response
CR	CR	No	CR
CR	Non-CR/Non-PD	No	PR
CR	Not evaluated	No	PR
PR	Non-PD or not all evaluated	No	PR
SD	Non-PD or not all evaluated	No	SD
Not all evaluated	Non-PD	No	NE
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD

If no technically adequate baseline imaging data are available for one or more regions (e.g. abdomen, thorax, pelvis), then:

- If no lesions are detected on follow-up scans of unavailable regions at baseline, then response assessment will be based on the available scans of the other regions.
- If one or more lesions are detected on follow-up scans of unavailable regions at baseline, then these lesions are regarded to be new lesions, resulting in an overall response of PD for this timepoint.
- If at a follow-up timepoint no technically adequate scans are available for one or more regions that were involved at baseline, and there is no evidence of progression on the available scans of other region, then:
    - If unavailable regions at a follow-up timepoint contain no target lesion, then response assessment will be based on the available scans of the other regions.
    - If one or more target lesions are located in unavailable regions at a follow-up timepoint, then an overall response of PD will be assigned at this timepoint. This assignment is subject to review and change before determination of the best overall response across all time points.

8.4 Best overall response

The best overall response is the best response recorded from the study start until the end of treatment across all time points. The best overall response will be derived from the assessments of overall response at the individual time points captured every 8 weeks in the CRF.

Once a CR is observed, any unequivocal reappearance of disease results in progression.

Once a PR is observed, the status remains PR until criteria for progression are met.

In patients with CR or PR, the date of response is the date when the criteria for CR or PR are first met.

If the response is not evaluable (e.g. target lesion difficult to visualize or evaluation not done) and there is no other evidence of PD at the time of evaluation, then the best overall response at that evaluation will be Not Evaluable (NE).

Early progression is defined as documented progressive disease that occurred in the first 8 weeks of treatment.

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 objective progression even after discontinuation of treatment. Symptomatic deterioration is not a descriptor of an objective response: it is a reason for stopping study therapy. The objective response status of such patients is to be determined by evaluation of target and non-target disease as shown in *Table 6* and *Table 7* above.

9 Assessment of safety

9.1 Adverse events

9.1.1 Reference documents

The product reference documents are:

***Nab*-paclitaxel:** Current version of the Investigator's Brochure, yearly updated.

Gemcitabine (marketed product administered on prescription in standard indication): Summary of Product Characteristics (SmPC) which can be found on:

http://www.ema.europa.eu/docs/en_GB/document_library/Referrals_document/Gemzar_30/WC500008487.pdf

Main risks and risk management for administering *nab*-paclitaxel and gemcitabine are detailed in *Section 5. Treatments*.

Printed or electronic versions of the reference documents will be provided to all investigators. Acknowledgements of receipt are required as per GCP.

Toxicity will be graded using the NCI CTCAE v. 4.0 available on:

http://www.eortc.be/services/doc/ctc/CTCAE_4.03_2010-06-14_QuickReference_5x7.pdf

9.1.2 Definitions

Adverse Event (or Adverse Experience) (AE):
An AE is any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavourable change and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

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.

Due to regulatory requirements, events occurring during pre- and post-treatment periods should also be designated as AEs. Therefore, safety surveillance (reporting of AEs) commences at the time when the patient is enrolled into the study (date of signature of the informed consent) until 30 days after the last dose of medication has been administered.

Therefore, events occurring in the period between the signature of the informed consent and beginning of treatment or within 30 days after stopping treatment are to be designated as AEs. This procedure complies with requirements by some authorities and insurance policies. Relationship with study treatments must always be carefully documented.

Adverse Drug Reaction (ADR)
All noxious and unintended responses to a medicinal product related to any dose should be considered adverse drug reactions (ADRs).

All adverse events judged by either the reporting investigator or the sponsor as having a reasonable causal relationship to a medicinal product qualify as adverse reactions. The expression reasonable causal relationship means to convey in general that there is evidence or argument to suggest a causal relationship.

Unexpected Adverse Reaction (UAR) is any adverse reaction, the nature, or severity of which is not consistent with the applicable product information (e.g. investigator's brochure for the study drug given in non-standard regimen or summary of product characteristics (SmPC) for products on prescription).

When the outcome of the adverse reaction is not consistent with the applicable product information this adverse reaction should be considered as unexpected.

Severity: The term “severe” is often used to describe the intensity (severity) of a specific event. This is not the same as “serious,” which is based on patient/event outcome or action criteria.

Serious Adverse Event (SAE) or Serious Adverse Reaction (SAR)

An SAE or SAR is any untoward medical occurrence that at any dose:

- results in death,
- is life-threatening,

NOTE: The term “life-threatening” in the definition of “serious” refers to an event in which the patient was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe.

- requires in-patient hospitalization or prolongation of existing hospitalization,
- results in persistent or significant disability/incapacity,
- is a congenital anomaly/birth defect, or
- is an important medical event.

Medical and scientific judgement should be exercised in deciding whether expedited reporting is appropriate in cases of important medical events that may not be immediately life-threatening or did not result in death or hospitalization but may jeopardize the patient or may require intervention to prevent one of the other outcomes listed in the definition above.

Examples of such events are intensive treatment in an emergency room, or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization; development of drug dependency or drug abuse; or malignant tumours when they are histologically different from the primary tumour.

Other events to be treated as SAEs:

- Exposure to drug during pregnancy/lactation.

In principle, pregnancy and the lactation period are exclusion criteria. In the event of a pregnancy occurring during the course of a study, the patient must be withdrawn from treatment immediately. The sponsor must be notified without delay and the patient followed during the entire course of the pregnancy and postpartum period. Parental and neonatal outcomes must be recorded even if they are completely normal and without AEs. The standard SAE report form should be used to report a pregnancy.

- Overdose and intoxication.

In the event of a drug overdose occurring in the course of the present study, this must be reported as a SAE.

- Misuse, abuse and occupational exposure

Events not treated as SAEs:

Progression of disease is not to be regarded as a SAE unless the disease progression is due to the study drug.

Due to the seriousness of the disease in this study, certain conditions defined as SAEs will be excluded from reporting on a SAE report form, i.e.:

- A standard procedure for protocol therapy administration. However, hospitalization or prolonged hospitalization for a complication of therapy administration will be reported as an SAE.
- A procedure for protocol or disease-related procedures (e.g., surgery, stenting, 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.
- Elective or planned hospitalization for treatment of a pre-existing condition.
- Death due to progression of disease not related to the study drug.

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.

SUSAR: Suspected Unexpected Serious Adverse Reactions

All suspected SAEs that are assessed as "Unexpected" not currently foreseen in the SmPC (for the medication on prescription) or in the IB (for study labelled medication) must be filed as SUSARs. The definitions and conditions of the SAE above apply.

Mortality within the first 60 days on trial will be reported.

9.1.3 Methods of recording and assessing adverse events

All AEs must be documented in the e-CRF under symptoms/toxicity/lab values. Severity and relationship to study treatment will be documented and taken into account in the analysis.

If in any one patient the same AE occurs on several occasions, then the AE in question must be documented and assessed and graded anew each time.

Among the AEs, all events that meet the "seriousness" criteria, SAEs and SAE follow up data *(See Section 9.1.1. Reference documents)* must be additionally documented in the SAE report form. A paper copy of the SAE report form must be kept in the Investigator's file. Any pertinent information recorded in the e-CRF in the AE section must be attached to the SAE report form, if applicable.

9.1.4 Procedure for reporting Serious Adverse Events

In the event of the occurrence of any clinical AE or abnormal laboratory test value that is serious or medically important or in the event of a pregnancy during the course of the study or the post-treatment period, irrespective of the treatment received by the patient, the investigator should immediately complete the pertinent data on the provided SAE report form and e-mail or fax it to the sponsor's assigned representative as instructed on the form and MOP.

Each study manager or study nurse will forward the completed SAE report form within 24 hours of receipt to the pharmacovigilance contact. This is to ensure that the initial reporting of SAEs to regulatory authorities is made within the requested timeframe.

As a principle, the SAE must be documented and medically assessed by the investigator in terms of severity (graded based on the NCI CTCAE v. 4.0) and relationship to treatment. The action taken, duration of event and outcome should be described and updated if applicable on the SAE report form and in the AE section of the e-CRF.

Where necessary, the SAE report form should be accompanied by other relevant pages from the CRF, e.g., for medical history, AEs, and concomitant drugs. If relevant, anonymized medical reports, lab reports or other documents allowing precise evaluation of the case may be joined or requested, including summary and/or complete translations in English when applicable.

The medical review of data will be performed by the sponsor or its delegates. Additional information or clarifications might be requested, if necessary, by the sponsor or its representatives or by the regulatory authorities, ethics committees or MAH. The investigator must provide the responses within the indicated timeframes.

The sponsor or appointed representative will set up, host and complete the pharmacovigilance database with all data submitted by the centers and will perform the regulatory requirements regarding SAE reporting as required by law.

The appointed CRO or representative will be in charge of expedited reporting to the competent authorities whenever applicable, in accordance with international and local laws and regulations. All SUSARs will be forwarded to all participating investigators, Celgene, ethics committees and the Eudravigilance CTM.

The appointed CRO or representative will provide an annual summary of all SAE reports for local submission purposes; the annual development safety report will be distributed to participating investigators and parties.

For further details, refer to the MOP.

9.2 Laboratory safety assessments

All clinical laboratory evaluations will be performed at the local laboratory of the investigational site complying with GCP and local requirements.

Hematology/chemistry laboratory parameters must be performed within 48 hours prior to each treatment administration. Treatment should not be administered if laboratory data are unavailable. If the patient's hematology data is not acceptable, treatment may be delayed for a maximum of two weeks.

A safety laboratory examination consisting of hematology and clinical chemistry must be performed at baseline and before each administration of *nab*-paclitaxel and/or gemcitabine.

Clinical laboratory tests are required at the "End of Treatment" visit and at the ""First Follow Up" visit". If treatment related toxicity persist after the "End of Treatment" visit, it must be followed until resolution. If severe related toxicity persists after the "End of Treatment" visit, laboratory assessments should be performed at least every 2 weeks until resolution.

CA19-9 and CEA must be performed at baseline, at each 8-weekly tumour (response) evaluation visit, at the "End of Treatment" visit.

Pregnancy test must be performed at baseline in women of childbearing potential then in accordance with local regulations. Women of childbearing potential must have a negative serum pregnancy test (minimum sensitivity according to local regulation) within 7 days prior the start of the medication.

Safety laboratory parameters:
Hematology (5 ml) (weekly except for the weeks of rest)

- Erythrocytes count, hemoglobin, hematocrit, white blood cell count, differential and platelet count.

Clinical Chemistry (10 ml) (weekly except for the weeks of rest)

- Glucose, total bilirubin, ALAT, ASAT, alkaline phosphatase, serum creatinine, total protein, sodium, potassium, chloride, serum calcium, blood urea and lactate dehydrogenase (LDH), CRP, routine coagulation.
- urine (standard dipstick and/or urinalysis) at baseline and when clinically indicated.
- magnesium (q8weeks)

Tumour markers (q8weeks)

- CA 19-9 level.
- CEA level.

Pregnancy test (if applicable) (within 7 days from start of treatment).
Male or female patients and their partners must be practicing a medically accepted contraception if applicable.

9.3 Vital signs, physical examinations, and other safety assessments

The following variables will be measured at baseline and periodically during the course of the study as applicable:

- physical examination (always comprises the following body systems: general appearance, skin, extremities, cardiovascular, pulmonary, abdominal, lymphatic or any other relevant clinical sign).
- WHO ECOG PS. *See Appendix 5: WHO ECOG PS scale.*
- vital signs
    - heart rate (after 5 minutes rest)
    - blood pressure (systolic/diastolic, supine, after 5 minutes rest)
    - body temperature
- weight/height
- cardiac examination: ECG (at baseline, EOT and when indicated)
- toxicity

10 Exploratory translational research

10.1 Background

SPARC (secreted protein, acidic and rich in cysteine) was found to be epigenetically silenced in pancreatic cancer cells but frequently expressed in the adjacent stromal fibroblasts. Nab-paclitaxel was thought to play an important role in enhancing paclitaxel delivery to the pancreatic tumor, by binding to SPARC in the stroma, thus facilitating gp-60–mediated endothelial transcytosis. A retrospective study found that patients with pancreatic cancer with high stromal SPARC expression had poorer survival than those with low expression (Infante, et al., 2007). In a phase II study with gemcitabine and nab-paclitaxel, a significant increase in OS was observed for patients in the high-SPARC group compared with patients in the low-SPARC group (Von Hoff, et al., 2011).

Human equilibrative nucleoside transporter 1 (hENT1) and deoxyctine kinase (dCK) are two metabolizing gemcitabine proteins and may play an important role in predicting clinical outcome of treatment with gemcitabine (Maréchal, et al., 2012), (Wei, Gorgan, Elashoff, Hines, Farrell, & Donahue, 2013), (Kahramanoğullari, Fantaccini, Lecca, Morpurgo, & Priami, 2012), (Skrypek, Duchêne, Hebbar, Leteurtre, van Seuningen, & Jonckheere, 2013), (Fujita, et al., 2010), (Tanaka, Javle, Dong, Eng, Abbruzzese, & Li, 2010), (Okazaki, M, Tanaka, Abbruzzese, & Li, 2010), (Ashida, et al., 2009), (Nakano, et al., 2007), (Giovannetti, et al., 2006).

S100A2 has been recently suggested as a negative prognostic biomarker in PAC. Among patients who received an adjuvant therapy, moderate/high levels of S100A2 were significantly associated with longer OS and DFS in multivariate, whereas low S100A2 levels were not (Bachet, et al., 2013).

Immunohistochemistry and q-PCR analyses for SPARC, hENT1, dCK and S100A2 expression are planned.

It has now clearly been demonstrated that hypoxia can induce epithelial to mesenchymal transition (EMT) and metastatic behaviour of cancer cells. Some hypoxia-induced modifications of gene expression in tissue might be prognostic of survival in hepatocellular carcinoma (van Malenstein, et al., 2010) or colon cancer (Dekervel & al, 2014). Hypoxia also influences epigenetic factors like promoter methylation in different cancers (Rawluszko, Bujnicka, Horbacka, Krokowicz, & Jagodzi Ski, 2013), (Hatzimichael, et al., 2010).

For the identification and validation of hypoxia-induced predictive biomarkers in pancreatic cancer we will investigate gene expression in tumour tissue and correlate results with promoter methylation in blood (Cen, Ni, Yang, Graham, & Li, 2012), using a PCR-based methylation-sensitive high resolution melting technique for accurate quantification of the methylation status (Hernández, Tse, Pang, Arboleda, & Forero, 2013).

10.2 Translational research objectives

The main translational research objectives of this trial are:

1. To study biomarkers that might inform on a predictive signature of response
2. To match mutation and expression data (to assess whether mutation status can in the future be used as a substitute for expression analysis).
3. To study molecular subgroups, gene pathways, signalling networks and potentially new molecular targets in pancreatic cancer.
4. To explore protein profiles in the development of resistance.

The analyses will focus on biomarkers that can be related with benefit to *nab*-paclitaxel:

- Potential SNPs
- Circulating DNA
- Circulating micro-RNA
- Selected cytokines (ELISA)
- hENT1, SPARC, dCK and S100A2 expression (immunohistochemistry/qPCR)
- Hypoxia induced biomarkers

10.3 Samples, timepoints, preparation and analyses

Sampling of blood is mandatory for all participating patients. If archived tissue is not available from a previous diagnostic biopsy or surgical specimen, the sampling of tumour tissue for translational research remains optional in consenting patients.

10.3.1 Blood and blood products

Samples:
Whole blood in EDTA tube 10 ml (baseline only)
Whole blood for plasma in EDTA tube 10 ml
Whole blood for serum in SST tube 10 ml

Timepoints:
Venous blood will be collected from all patients at 3-4 timepoints depending on the Arm, *see*

Figure 2: Translational research timepoints – **overview**:

Baseline: 3x10ml (whole blood, plasma and serum)
Week 9: 2x10ml (plasma and serum)
Cross-over: 2x10ml (plasma and serum). Only from patients in Arm B eligible to cross-over.
Progression: 2x10ml (plasma and serum). If patients discontinued for reasons other than progression or death, these blood samples will be collected immediately or within a maximum of 30 days after treatment discontinuation but before any other treatment.

Preparation:
Whole blood tube (baseline only):

- No centrifugation.
- Store as is at –80°C.

EDTA tube for plasma:

- Centrifuge 10 minutes at 2000g (4°C).
- Transfer 3 x 1.5 ml plasma to 2 ml vials.
- Discard pellets in EDTA tube.
- Store aliquots at -80°C.

SST tube for serum:

- Wait until the blood is clotted: 20-60 minutes at room temperature.
- Centrifuge 10 minutes at 2000g (4°C).
- Transfer 3 x 1 ml serum to 1.5 ml vials.
- Store aliquots at -80°C.

Analyses:
Whole blood at baseline only for:

- Analysis of potential SNPs that might correlate with benefit to *nab*-paclitaxel

Plasma for:

- Circulating micro-RNA
- Circulating DNA
- Selected cytokines (ELISA)

Serum for:

- Hypoxia-induced biomarkers
- Circulating micro-RNA

The actual date and time of sampling and number of samples obtained will be documented in the e-CRF. Detailed description of sampling, labelling, processing, storage and shipment of specimens could be found in the MOP.

10.3.2 Tissue

Archived tissue (paraffin embedded) from a previous diagnostic biopsy or surgery is required when available, in form of blocks (that can be returned to the hospital of origin) or minimum 15 slides. If archived tissue is not available, consenting patients may provide tissue samples taken by core needle biopsy collected either endoscopically during EUS or percutaneous under ultrasound or CT control before the start of treatment. Tissue collected by biopsy will be formalin fixed and embedded in paraffin at the site, then the block (preferred) or minimum 15 slides will be shipped to U.Z. Leuven.

Patients will be informed in a verbal and written form about the procedures of biopsy taking. An addendum to the main informed consent will be presented to patients for the purpose of biopsies.

Previously archived tissues or biopsy samples shall be used for:

- Immunohistochemistry analysis / qPCR for hENT1, SPARC and dCK expression.
- Hypoxia studies

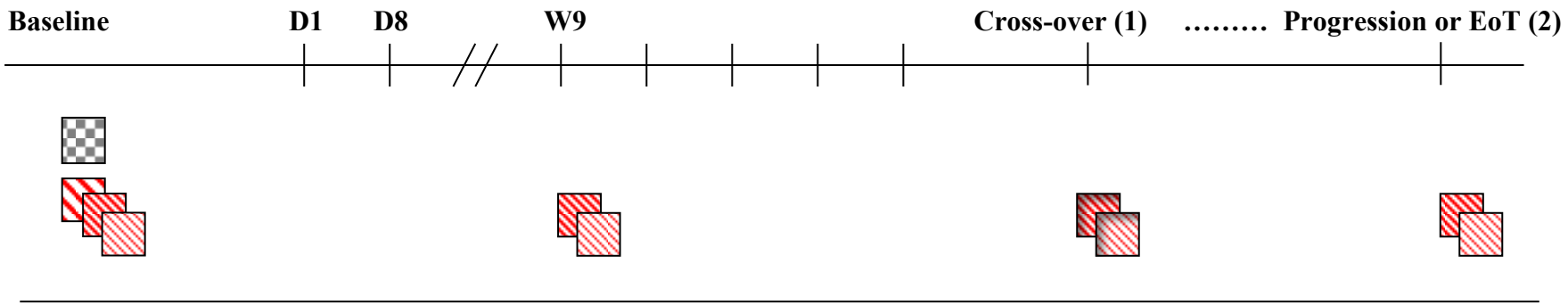
In the context of this protocol a biopsy sample is defined as the entire quantity of tumour material obtained after one pass of the biopsy needle (core, not fine needle).

Fine needle biopsy aspirate (cytology) is not acceptable.

The actual date and time of biopsy taking and number of samples obtained will be documented in the e-CRF. Detailed description of the biopsy sampling, labelling, processing, storage and shipment of specimens could be found in the MOP.

All analyses will be performed by U.Z. Leuven.

Figure 2: Translational research timepoints – overview



Legend:

- Previously archived tumour tissue or FFPE biopsy samples (from consenting patients) – blocks (preferred) or min 15 slides
- 10 ml whole blood in EDTA tube (pre-infusion, baseline only) –stored at -80°C
- 10 ml blood for plasma in EDTA tube (pre-infusion) – 3x1.5 ml cryovials stored at -80°C
- 10 ml blood for serum in SST tube (pre-infusion) – 3x1 ml cryovials stored at -80°C

(1) Patients in Arm B who crossed-over to combination Arm only: TR blood samples to be collected before first nab-paclitaxel infusion.
(2) Patients that were taken off study for other reasons than progression or death: TR blood samples to be collected immediately or within 30 days from discontinuation, but before starting of any new treatment.

11 Statistics

11.1 Primary variables

The deterioration free survival rate at 3 months is defined as the Kaplan-Meier estimate of the probability of being alive and free of deterioration of the QOL scores at 3 months. The deterioration of the QOL score is a decrease of at least 10 points (minimal clinical important difference) between the score at baseline and any timepoint. The time interval will be calculated from the time of completion of the baseline QOL questionnaire.

The deterioration free rate at 3 months, comparatively in both treatment Arms is the study primary variable.

QOL scoring

For ease of statistical interpretations and psychometric validation, all scale and item scores entered by patients will linearly be transformed to a scale from 0 to 100.

A high score for a functional scale represents a high / healthy level of functioning.
A high score for the global health status / QOL represents a high QOL.
A high score for a symptom scale / item represents a high level of symptomatology / problems.

Scoring procedures and use with main statistical packages are provided by EORTC (Fayers, et al., 2001), (Scott, et al., 2008).

Definitions

Each patient will have a set of reference baseline scores: per scale as described above (general health, functional, symptom etc.). These will be used to calculate mean changes from baseline to each timepoint when the questionnaire is completed (i.e. every four weeks).

Osoba et al. (Osoba, Rodrigues, Myles, Zee, & Pater, 1998) showed that a mean change (from baseline to the timepoint considered) of 5 to 10 points in a QLQ-C30 score corresponds to a "little" change in QOL, a change of 10 to 20 points corresponds to a "moderate" change and change of more than 20 points corresponds to a "large" change.

We will use the 10 point difference as cut off for "minimal clinically important difference" for changes observed. Clinically significant definitive deterioration is indicated when a certain score decreases by 10 points as compared to baseline, without later improvement of at least 10 points when compared to baseline or without any further available score.

TUDD for QOL scores is defined as the time from baseline questionnaire to the first observation of a definitive deterioration of a QLQ-C30 score.

TUDDs will be calculated and analysed for each scale: TUDD of the general health, functional and symptom TUDDs.

11.2 Secondary variables

11.2.1 Efficacy variables

Progression free survival (PFS)

Progression free survival is defined as the time from Day 1 of therapy (day of first infusion of medication on study), until the first observation of disease progression (documented by appropriate imaging techniques) or the date of death due to any cause, if death occurred within 60 days after the last valid tumour assessment.

For patients who deceased more than 60 days after either the last valid tumour assessment or after the date of Day 1 of therapy without having had imaging performed, the PFS time will be censored on the date of last tumour assessment or date of Day 2 of therapy respectively.

Non-progressed patients discontinuing study treatment and not undertaking a different anti-cancer treatment will be censored for progression at the date of the last valid tumour assessment.

Non-progressed patients discontinuing study treatment and undertaking a different anti-cancer treatment will be censored for progression at the date of starting the new anti-cancer treatment. Exceptions of this rule may be applied for patients undertaking procedures that are not aimed at the main disease i.e. stenting, radiotherapy for symptom control not on target lesions, and possibly other treatments on a case by case basis.

Overall survival time

The survival time of a patient is defined as the time from Day 1 of therapy to death. For patients who are still alive at the time of study analysis or who are lost to follow up, survival will be censored at the last recorded date that the patient is known to be alive or at the date of data cut-off, whatever occurs earlier.

Overall response

Tumour (response) evaluation will be performed at baseline (within 28 days from treatment start) and every 8 weeks afterwards, according to RECIST criteria v. 1.1 (CT scan or MRI). The overall response rate is the percent of patients achieving a best response of either CR or PR (CR+PR).

Disease control

The disease control rate is the percent of patients achieving a best response of either CR, PR, or SD (CR+PR+SD).

Duration of response

The duration of response in responding patients is defined as the time interval from the time measurement criteria are first met for CR/PR to either the first time disease progression is documented or death (for not progressed patients who deceased within 60 days from last tumour assessment). The duration of response will be censored on the date of last known tumour assessment for not progressed patients lost to follow up or deceased prior to the next planned tumour assessment (within 60 days). Not evaluable patients at one time point assessment will be censored at the date of last known assessment.

11.2.2 Safety variables

Safety and tolerability will be assessed throughout the study by evaluating the following safety variables:

- Adverse events throughout the study for which the following data are to be recorded:
    - Description
    - Start and stop date and time
    - NCI-CTCAE v. 4.0 grade. *See Appendix 2: NCI-CTCAE v.4.0.*
    - Causal relationship with medication
    - Action taken
    - Outcome
    - Seriousness
    - Expectedness.

- Laboratory safety assessments performed as specified in Section *6. Methodology and study procedures*. They are mandatory prior to the administration of study medication. They are required at the End of Treatment visit and the First Follow Up visit. Pregnancy test is performed within 7 days from start of treatment if applicable. The tumour markers CA 19-9 and CEA are measured at baseline, at each 8-weekly tumour (response) evaluation visit, and at the End of Treatment visit. The following clinical safety tests are foreseen:
    - Hematology: Erythrocytes, hemoglobin, hematocrit, white blood cell count, differential, and platelet count.
    - Chemistry: Glucose, total bilirubin, ALAT, ASAT, alkaline phosphatase, serum creatinine, total protein, sodium, potassium, magnesium (q8weeks), chloride, serum calcium, blood urea, and lactate dehydrogenase, CRP, routine coagulation tests.
    - Urine dipstick at baseline and when clinically indicated.
- Vital signs, physical examination, ECG, and WHO ECOG performance status (PS) are recorded.

11.3 Analysis sets

The following analysis sets are considered:

Intent to treat total set (ITT):	All patients who consented to participate in the study.
Safety Set (SS):	All patients for whom there is evidence any dose of *nab*-paclitaxel and/or gemcitabine on study had been administered.
Per Protocol Set (PPS):	All patients receiving treatment without any major protocol deviation.

The primary set for the quality of life analysis is the ITT. A sensitivity analysis of the primary variables and of PFS will be performed on the basis of the PPS.

Subgroup analyses:

A minimization technique [minimizing imbalance in the distributions of treatment numbers within the levels of each individual prognostic factor (Pocock & Simon, 1975)] will be used for random treatment allocation stratifying by the following factors:

- Center
- WHO ECOG performance status (0 and 1 versus 2)
- Location of tumour (head of the pancreas versus other location)
- Stage (locally advanced versus metastatic disease)

The following subgroups are considered for key analyses:

- Gender: female, male.
- Age: <70 and ≥ 70.
- Location of the tumour: head of the pancreas versus other locations.
- Stage: locally advanced versus metastatic disease
- WHO EGOC PS at baseline: 0 and 1 versus 2
- Arm A, Arm B and cross-overs.

11.4 Statistical design

11.4.1 Sample size

The sample size calculation is based on the deterioration of the global health score (*See Section 7.1. Structure of the questionnaire)* 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.

The hypotheses for sample size calculations are based on the results of the QOL analysis of the PRODIGE/ACCORD 11 trial (Gourgou-Burgade, et al., 2013). In this publication, the curves of TUDD comparing folfirinox and gemcitabine show that the percentages of patients free from definitive deterioration of the global health score at 3 months were 83% in Folfirinox Arm and 69% in the gemcitabine Arm.

Assuming similar results for the *nab*-paclitaxel + gemcitabine Arm versus gemcitabine alone, these percentages are used as hypotheses for sample size calculations for the present study. A 3-month deterioration free rate of the global health score of 83% for *nab*-paclitaxel + gemcitabine Arm and of 69% for gemcitabine Arm are assumed for calculating the sample size using a log-rank test.

Statistical assumptions for sample size calculation:

Hypotheses :

a. 2-sided alpha=0.05
b. power=80%
c. accrual 8-9 pts per month
d. 3-months deterioration free rate of 83% for *nab*-paclitaxel + gemcitabine
e. 3-months deterioration free rate of 69% for gemcitabine monotherapy

Results:

a. Accrual duration: 12-14 months
b. Total study duration 21 months
c. Total sample size N=100
d. Number of events E=68 (number of patients with definitive deteriorations)

The drop-out rate is defined as the proportion of patients that failed to provide at least one QOL questionnaire at the end of treatment. We assume a 30% drop-out rate at the end of study which is in line with current EORTC recommendations on QOL studies.

To reach the number of events estimated at point d. of the sample size calculation above and considering a 70% patient compliance in providing post-treatment QOL data (30% drop-out rate) an increase of the initial sample size to 143 patients (100/0.7=142.86 =~143) is required for reaching the main endpoint of the study.

11.4.2 Statistical analysis - general considerations

The statistical analysis will be performed using the SPSS statistical package, version 11.0 or later. All analyses will be performed separately for the Arm A and Arm B data. Cross-over patients will be also described separately in a subgroup analysis. There will be no statistical tests or models to compare efficacy or safety between the two Arms. For the

QOL data, an analysis of data missingness will be performed. There will be no imputation of missing efficacy or safety data in the secondary analyses.

The statistical analysis will consist of:

- Descriptive statistics for quantitative variables consisting of the mean, standard deviation, 95% CI of the mean, minimum, Q1, median, Q3, maximum, and number of observations. For categorical variables frequencies and percentages will be given for all values or categories. Exact 95% Clopper-Pearson confidence intervals will be provided for key categorical variables.
- Kaplan-Meier analysis of time to event variables.
- Multivariable analysis of time to event variables by means of Cox proportional hazards. The independent variables to be used will be specified in the final Statistical Analysis Plan.

All analyses are regarded as exploratory therefore no significance level is fixed.

11.4.3 QOL analyses

The QOL data obtained from the patient population will be analysed following the EORTC guidelines (Fayers, et al., 2001), (Scott, et al., 2008).

Several types of statistical analyses will be performed:

Longitudinal analysis of data. Changes of mean QOL scores during treatment and follow up will be assessed descriptively in both Arms. Comparison between baseline and the end of treatment will be performed using the sign rank test. The internal consistency of the questionnaire will be estimated by using the Cronbach's alpha for each dimension and visit.

Time Until Definitive Deterioration analysis. TUDDs will be determined according to a minimal clinically important difference (MCID) of at least 10 points in QLQ-C30 scores for the different domains in both Arms using a time to event analysis (Kaplan-Meier). The log-rank test will be used to compare treatment Arms. TUDDs will be alternately analysed using a MCID of 20 points and integrating death as an event.

Analysis of variance. Multivariate analyses will be used to determine baseline prognostic factors for overall survival, following the method published by EORTC (ref meta-analysis)

Analysis of compliance and missingness of data. Missing questionnaires will be accounted for in a descriptive manner. Reasons will be summarized per Arm and type.

11.4.4 Efficacy analyses

The statistical analysis of efficacy will consist of:

- Kaplan-Meier analysis of PFS, OS and duration of response.
- Multivariable analysis of PFS and OS by means of Cox proportional hazards.
- Estimate with exact 95% confidence interval of best overall response rate and disease control rate.
- Descriptive analysis of the relationship between time to progression and TR data.

11.4.5 Safety analyses

Safety analyses will be performed on the basis of the Safety Set. No formal statistical comparisons between Arms are planned on the secondary variables.

The **extent of exposure** to *nab*-paclitaxel and gemcitabine will be characterized per treatment group by duration (weeks), number of infusions, cumulative dose (mg/m²), dose intensity (mg/m²/week), relative dose intensity (actual dose given/planned dose), number of dose reductions, and number of dose delays.

AEs will be graded according to NCI-CTCAE toxicity criteria v. 4.0. and coded according to the Medical Dictionary for Regulatory Affairs (MedDRA) current version. The analysis of AEs will only consider treatment-emergent AEs, defined as AEs with an onset date on or after Day 1 of study therapy and up to the End of Treatment visit within one month from treatment discontinuation. Frequencies will be given of patients with AEs, SAEs, related AEs, related SAEs, AEs leading to withdrawal, dose modification or discontinuation of treatment, broken down by treatment group. The frequency of patients with AEs will be provided:

- Broken down by system organ class, preferred term, and maximal NCI-CTCAE v 4.0 grade.
- Broken down by system organ class, preferred term, grade and relationship to treatment. AEs reported with a causal relationship of "definitely related", "possibly related" and "unknown relationship/not assessable" to medication will be considered related to treatment. In case of missing relationship assessment AEs will be considered as related to the treatment.

Frequency distributions will be provided for all deaths, deaths within 60 days after first dose, and death within 30 days after last dose of study treatment.

Laboratory results will be classified according to the NCI-CTCAE v. 4.0. The worst on-study grade after the first treatment dose on study will be summarized. Incidence of NCI-CTCAE v. 4.0 grade 3 or 4 laboratory abnormalities under treatment.

Clinically significant abnormal findings from the physical examination and vital sign measurements are to be reported as AEs. Therefore, no separate summaries will be provided of the physical examination data.

11.4.6 Interim analyses

Six monthly safety analyses have been planned.

11.4.7 Reporting deviations from the analysis plan

Deviations from the analysis plan, along with the reasons for the deviations, will be described in annual reports, eventual protocol amendments, the complete statistical plan, the clinical study report, or any combination of these, as appropriate.

12 Study management

12.1 Electronic case report form

The appointed developer will be responsible for creating and hosting a functional electronic platform for data collection in conformity with standard regulations. Staff and assigned representatives from each site will gain access to the electronic forms upon site registration and after the required investigator authorizations and site agreements have been signed.

An electronic CRF entry for every subject participating in the clinical study is mandatory and will be individually created by the investigator or assigned study nurse by using the provided electronic platform.

The main objective is to obtain the required data in a complete, accurate, legible, verifiable and timely fashion. The data in the e-CRF should be consistent with the relevant source documents. Printable formats will be available for use and filing, if needed. However, all data recorded in the course of this study must be timely documented in the electronic CRF to allow for prompt processing and evaluations. Automated verification checks will be built within the electronic platform for continuous monitoring purposes.

All data will be stored anonymously in accordance with the data-protection regulations.

Each investigator must ensure that the data is regularly updated and that the timescales specified for SAE reporting are respected.

Any amendments and corrections necessary must be undertaken by the investigator or designated staff. All modifications will be electronically tracked in an audit trail. The investigator or staff must state his/her reasons for the correction of important data in comments or as response to the data clarification requests.

In the case of missing data/remarks, the entry spaces provided for in the e-case report form will be highlighted. Follow-up inquiries will be programmed and performed automatically. In case missing data cannot be completed, the investigator or nurse must state a reason to avoid further monitoring queries.

The completed e-CRF will be printable, totally or partially if needed. Relevant pages should accompany the SAE report. Printing (on paper or as .pdf files saved on CD-roms) of all CRF data entered electronically will be needed for archiving requirements at the end of the study. The electronic CRF platform will be maintained active and opened for data entry 9 months after the last patient's "First Follow-Up" visit. Afterwards, disease and survival follow up data will be updated on simplified local and central files. Instructions will be provided in the MOP and its appendices.

12.2 Source data and subject files

The available demographic and medical information of a subject transcribed in the CRF has to be retrievable in source documentation (subject medical file), in particular the following: year of birth, sex, height, weight, subject history, concomitant diseases and concomitant drugs (including changes during the study), statement of entry into the study, study identification, subject number, the date of informed consents, all study visit dates, predefined performed examinations and clinical findings, observed AEs (if applicable), reason for withdrawal from the study if applicable, etc. It should be possible to verify the inclusion and exclusion criteria for the study from the available data in patient's medical file.

Additionally, any other data transcribed in the CRF (i.e. lab results or other automated testing reports) or data recorded on printed forms used to collect patient information at the time of visits will be filed in or retrievable from source documentation.

12.3 Investigator Site File, Pharmacy file and archiving

The investigator will be provided with an investigator site file (ISF) and a Pharmacy file at the start of the study. These files contain all relevant documents necessary for the conduct of the study and drug accountability, respectively. These files must be safely archived after the termination of the study.

It is the responsibility of the investigator to ensure that the patient-identification sheets are stored for at least 20 years beyond the end of the clinical study. All original patient files must be stored for the longest possible time permitted by the regulations at the hospital,

research institute, or practice in question. If archiving can no longer be maintained at the site, the investigators will notify the sponsor.

12.4 Monitoring, Quality Assurance and inspection by authorities

This study is to be conducted in accordance with the International conference of Harmonization (ICH) Note for Guidance on Good Clinical Practice (ICH, Topic E6, 1995) dated July 17, 1996 and the Ethical Principles for Medical Research Involving Human Subjects in the WHO Declaration of Helsinki.

Further to automated verification checks and monitoring queries built in the electronic platform, appointed clinical monitors will perform regular visits to the participating center(s) on a regular basis. Detail description can be found in the monitoring guidelines and MOP.

In line with ICH GCP guidelines monitoring will include verification of data entered in the e-CRFs against original patient records. This verification will be performed by direct access to the original patient records and the sponsor/appointed CRO guarantees that patient confidentiality will be respected at all times. Participation in this study will be taken as agreement to permit direct source data verification. Data generated at the pre-screening visit are verified against source data only in case the patient enters the study.

In addition, the representatives of the sponsor, Clinical Quality Assurance department at Celgene, their appointed monitoring organizations, and international regulatory authorities are permitted to inspect the study documents (study protocol, case report forms, medication, original medical records/files). All patient data shall be treated confidentially.

The study protocol, each step of the data-recording procedure, and the handling of the data as well as the study report could be subject to the independent Clinical Quality Assurance by Celgene. Audits can be conducted to assure the validity of the study data.

12.5 Changes to the study protocol

Changes to, or formal clarifications of, the study protocol must be documented in writing.

Changes to the protocol will be described in a "Protocol Amendment". All amendments will be submitted to the relevant ECs and to authorities where required.

Approval/favourable opinion from the relevant ECs will be required prior to implementation of the amendment.

Amendments will be signed by all signatories of the protocol.

All investigators will acknowledge receipt and confirm by their signature on the Amendment Signature Sheet that they will adhere to the change. This sheet will be issued in duplicate and after signing one will be filed in the Investigator Site File and one in the Study Master File.

Any Amendment affecting the patients requires the subjects' informed consent prior to implementation.

12.6 Study report and publication policy

After the database lock and analysis, the sponsor will produce the integrated study report. The first publication will be a full publication of all data of all sites. Any publications of the results, either in part or in total (abstracts in journals or newspapers, oral presentations, etc.) by investigators or their representatives will require pre-submission review by the Sponsor.

The Sponsor is entitled to delay publication if justified. First author of the first original article in an appropriate journal is the principal investigator Prof. Dr. E Van Cutsem. Co-authors will be the members of the writing committee and investigators who have recruited patients to the study. The order of co-authorship will be defined according to the recruitment rate of the investigational centers and intellectual/scientific input. The number of co-authors will be determined by the type of publication and the criteria set by the respective journal or conference board.

A publication plan for multiple publications will be set up together with the investigators.

13 Ethical and regulatory aspects

13.1 Responsibilities of the Investigator

The investigators shall be responsible for ensuring that the clinical study is performed in accordance with the protocol, the ethical principles that have their origin in the Declaration of Helsinki (World Medical Association Declaration of Helsinki) as well as with the International Conference on Harmonization of Technical Requirements of Pharmaceuticals for Humans Use (ICH) Note for Guidance on Good Clinical Practice (ICH, Topic E6, 1995) approved July 17, 1996 and applicable regulatory requirements.

13.2 Subject information

An unconditional prerequisite for a subject participating in the study is his/her written informed consent. Adequate information must therefore be given to the subject by the investigator before informed consent is obtained. A person designated by the investigator may give the information, if permitted by local regulations. A subject information sheet in the local language and prepared in accordance with the ICH Note for Guidance on Good Clinical Practice (ICH, Topic E6, 1995) will be provided by investigator for the purpose of obtaining informed consent. In addition to this written information, the investigator or his designate will inform the subject verbally. In doing so, the wording used will be chosen so that the information can be fully and readily understood by laypersons.

The subject information sheet will be revised whenever important new information becomes available that may be relevant to the consent of subjects. The amendments to consent forms should be presented to all participating patients.

13.3 Subject consent

13.3.1 Informed consent procedures

If the patient is eligible (*See Inclusion/Exclusion criteria and definition of eligibility*), the study information and consent forms will be presented, *see Patient information and consent form*. Local approved versions of these documents are available in each national language (French and Dutch) – submitted separately.

If patient agrees to the participation into the trial, the signature of the participant and of the investigator conducting the study will be collected prior to any study-related procedures. The signature of the patients means he/she agrees to participate in the study, provide blood samples for translational research and allow previously archived tissue (if available) to be sent and analysed by U.Z. Leuven.

Additional information and consent pages for tissue biopsies are to be presented to patients from whom no previously archived tumour tissue is available. Although the biopsy at

baseline remains optional, it is recommended that investigators make every effort to provide tumour tissue for translational research studies.

Provision of consent and type of consent (i.e. participation in the clinical trial and agreement for biopsy if applicable) will be confirmed in the e-CRF by the investigator. The signed and dated original declaration of informed consent will remain at the investigators' site and must be safely archived by the investigator so that the forms can be retrieved at any time for monitoring, auditing and inspection purposes. A copy of the signed and dated information and consent should be provided to the subject prior to study start.

13.3.2 Witnessed informed consent

Illiterate subjects
If the subject is unable to read, a reliable and independent witness should be present during the entire informed consent discussion. The choice of the witness must not breach the subject's right to confidentiality. A reliable independent witness is defined as one not affiliated with the institution or engaged in the investigation. A family member or acquaintance can be appropriate independent witnesses.

After the subject orally consents and has signed, if capable, the witness should sign and personally date the consent form attesting that the information is accurate and that the subject or has fully understood the content of the informed consent agreement and is giving true informed consent.

13.4 Compensation to subjects

Insurance coverage will be provided by the sponsor for all subjects enrolled in the study from the time of subjects' inclusion into the study (i.e. date of signing consent or screening visit). Insurance confirmations, policies and certificates are made available to participating centers and filed in the investigator site file.

No financial benefit or incentive to participate will be offered to patients neither by the sponsor nor by Celgene.

13.5 Ethics Committee or Institutional Review Board

Prior to commencement of the study, the study protocol will be submitted together with its associated documents (patient information, consent form, investigator's brochure) to the relevant ethics committees (ECs) or institutional ethics review boards for their favourable opinion. The favourable opinion/approval of the ECs will be filed in the investigator site file and a copy in the trial master file handled by the sponsor.

The study will only commence following provision of a written favourable opinion from central EC after consultation with all local ECs as per national practices.

Any document arising from an Ethics Committee meeting, such as date of the meeting, name of people attending the meeting, voting members, comments, remarks will be collected and filed in the proper section of the trial master file handled by the sponsor. Written evidence that clearly identifies the protocol version, and consent documents reviewed by ECs will also be filed.

Any amendments to the protocol will be submitted to the EC and they will be informed about SAEs in accordance with national and/or local requirements (development safety update reports).

All submission procedures and necessary documentation including translations in national languages of the information sheet and patient informed consent will be performed by the sponsor and delegates.

13.6 Notification to authorities

The study protocol and applicable documentation (subject information, consent form, quality of life questionnaire, etc.) will be notified to authorities in accordance with the European regulations and/or the laws of Belgium.

14 Trial sponsorship and financing

U.Z. Leuven is the legal sponsor for all participants and is represented by the central PIs for the purpose of this study

Contract and subcontracting information for participants/investigator fees and invoicing:

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Celgene International sarl provides a research grant and supplies study labelled Abraxane® (*nab*-paclitaxel) for the conduct of this trial in all participating centers.

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Investigator signature page

Protocol title:

Randomized crossover trial to assess the effects and quality of life in patients with locally advanced or metastatic pancreatic cancer treated with gemcitabine in combination with *nab*-paclitaxel: QOLINPAC

EudraCT # 2013-004101-75;
U.Z. Leuven reference # S56122

Date/Version number of the protocol:08/06/2015 – Version 3.0

Name, academic degree of the site PI:

Site number:

Hospital/Institution

Address:

Telephone:

Fax:

e-mail address:

I, the undersigned, am responsible for the conduct of the trial at this site and affirm that:

I understand and will conduct the trial according to the clinical trial protocol, any approved protocol amendment, ICH Good Clinical Practice (ICH Topic E6 GCP) and all applicable Health Authority requirements and national laws.

I will not deviate from the clinical trial protocol without prior written permission from the Sponsor and prior review and written approval from the Institutional Review Board or Ethics Committees, except where necessary to prevent immediate danger to the subject.

Date: ..... Signature: .....

Appendices