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Title: A Multicenter Randomized Phase II Study of NPC-1C in Combination with Gemcitabine and nab-Paclitaxel versus Gemcitabine and nab-Paclitaxel alone in Patients with Metastatic or Locally Advanced Pancreatic Cancer Previously Treated with FOLFIRINOX

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Investigational Agents:

Drug Name:	NPC-1C antibody (NEO-102), Ensituximab
IND Number:	100207
Sponsor:	PRECISION BIOLOGICS, Inc.
Manufacturer:	Cytovance Biologics

Précis

Background:

- Pancreatic cancer carries a poor prognosis with an overall 5-year relative survival rate of 5-6%. In a recent Phase III trial the regimen of FOLFIRINOX has shown an encouraging outcome compared to Gemcitabine leading to the use of FOLFIRINOX as a first line treatment option for patients with advanced pancreatic cancer. Similarly, the combination of gemcitabine and paclitaxel protein-bound particles for injectable suspension (albumin-bound) (nab-Paclitaxel, ABRAXANE®) has demonstrated phase III survival benefit and has been FDA approved for the first-line treatment of pancreatic cancer. There are currently no data for either Gemcitabine/nab-Paclitaxel or FOLFIRINOX in the second-line setting. However a common extrapolation from the first-line studies has led many in the community to sequence FOLFIRINOX treatment followed upon disease progression by Gemcitabine/nab-Paclitaxel for patients with advanced pancreatic cancer with good performance status.
- NPC-1C is a chimeric monoclonal IgG1 antibody recognizing an epitope in the polypeptide backbone of aberrantly glycosylated MUC5AC.

Objectives:

- Phase I Primary Objective
  - To determine the safety and tolerability of NPC-1C (NEO-102) monoclonal antibody therapy in combination with Gemcitabine as a second line therapy in subjects with metastatic, locally advanced unresectable or recurrent pancreatic cancer previously treated with FOLFIRINOX and whose tumors bind NPC-1C by at least 20% on IHC. **COMPLETED.**
- Phase IIB Primary Objective
  - To determine whether NPC-1C (NEO-102) in combination with Gemcitabine and nab-Paclitaxel will increase the overall survival (OS) compared to Gemcitabine and nab-Paclitaxel alone in patients with metastatic, locally advanced unresectable or recurrent pancreatic cancer previously treated with FOLFIRINOX and whose tumors bind NPC-1C by at least 20% on IHC.
  - Secondary Objective

    To determine the safety and feasibility of NPC-1C (NEO-102) in combination with Gemcitabine and nab-Paclitaxel in patients with metastatic, locally advanced pancreatic cancer previously treated with FOLFIRINOX.

Eligibility:

- Subjects with measurable recurrent, locally advanced unresectable or metastatic adenocarcinoma of the pancreas who have progressed after primary therapy; subjects must have progressed after receiving FOLFIRINOX or were intolerant of FOLFIRINOX (or FOLFIRINOX-like regimen).
- IHC: ≥ 20% of tumor on tissue sections must stain with NPC-1C.

- Age: ≥ 18 years of age.
- ECOG Performance status of 0-1.

Design/Schema:

- This is a randomized phase II multi-institution prospective open label study in which up to 90 evaluable subjects with measurable metastatic, locally advanced unresectable or recurrent pancreatic cancer who failed or did not tolerate chemotherapy with FOLFIRINOX will be enrolled into one of two arms, A and B.

Arm*	**Gemcitabine (mg/m^2 IV on days 1, 8, and 15 of a 28-day cycle)**	**Nab-paclitaxel (mg/m^2 IV on days 1, 8, and 15 of a 28-day cycle)**	**NPC-1C** (NEO-102) **(mg/kg IV every other week on days 1 and 15 of a 28-day cycle)**
A	1000	125	1.5
B	1000	125	No NPC-1C
*Patients will be randomized between Arms A and B.			

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1 INTRODUCTION

1.1 STUDY OBJECTIVES

1.1.1 Primary Objectives

- To determine whether NPC-1C (NEO-102) in combination with Gemcitabine and paclitaxel protein-bound particles for injectable suspension (albumin-bound) (nab-Paclitaxel, ABRAXANE®) will increase the overall survival (OS) compared to Gemcitabine and nab-Paclitaxel alone in patients with metastatic, locally advanced pancreatic cancer previously treated with FOLFIRINOX or (FOLFIRINOX-like regimen) and whose tumors bind NPC-1C by at least 20% on IHC.

1.1.2 Secondary Objectives

To determine the safety and feasibility (as measured by futility and efficacy) of NPC-1C (NEO-102) in combination with Gemcitabine and nab-Paclitaxel in patients with metastatic, locally advanced pancreatic cancer previously treated with FOLFIRINOX or FOLFIRINOX-like regimen.

- To determine the safety and tolerability of NPC-1C(NEO-102) monoclonal antibody therapy in combination with Gemcitabine in subjects with metastatic, locally advanced unresectable or recurrent pancreatic cancer who failed or did not tolerate first line chemotherapy of FOLFIRINOX and whose tumors bind NPC-1C. COMPLETED

1.1.3 Secondary Objectives

- To determine the progression free survival (PFS) and response rate (RR) of patients with metastatic or locally advanced unresectable or recurrent pancreatic cancer who progressed following or did not tolerate chemotherapy of FOLFIRINOX or FOLFIRINOX-like regimen when receiving the combination of NPC-1C(NEO-102) monoclonal antibody, Gemcitabine and nab-Paclitaxel.
- To explore the immunologic correlates associated with the administration of NPC-1C (NEO-102) monoclonal antibody therapy in combination with Gemcitabine and nab-Paclitaxel.

1.2 BACKGROUND AND RATIONALE:

1.2.1 Pancreatic cancer

It is estimated that 43,920 patients will be diagnosed with pancreatic cancer and 37,390 patients will die from the disease in 2012 [1]. Pancreatic cancer carries a poor prognosis with an overall 5-year relative survival rate of 5-6% [2] [3]. Surgery remains the only chance for cure for patients diagnosed with resectable disease, however, only 10% of the patients present with operable disease [4]. Gemcitabine has been considered the first line therapy for advanced pancreatic cancer for the last 2 decades due to its efficacy in alleviation of disease-related symptoms and modest effect on overall survival (median OS 5.65 months) [5]. However, recently the regimen of FOLFIRINOX

has shown an impressive outcome compared with Gemcitabine in a Phase III trial; median overall survival was 11.1 months in the FOLFIRINOX group compared to 6.8 months in the Gemcitabine group (hazard ratio for death, 0.57; 95% CI, 0.45 to 0.73; P<0.001). The study was restricted to patients with performance status of 0-1 and FOLFIRINOX was associated with an increased toxicity but better quality of life at 6 months. [6]. Patients who received Gemcitabine as a second line after they progressed on FOLFIRINOX had a median overall survival of 4.4 months. Based on these findings, FOLFIRINOX has emerged as a first line treatment for patients with advanced pancreatic cancer who have a good performance status [7].

In the era of targeted therapy many agents have been combined with Gemcitabine as a backbone in advanced pancreatic cancer but with disappointing efficacy. The addition of Erlotinib (anti-EGFR antibodies) to Gemcitabine has increased the survival over Gemcitabine alone by 0.5 months only, which led to the FDA approval of this combination in the treatment of metastatic or locally advanced pancreatic cancer [8]. Other clinical trial efforts for the treatment of metastatic pancreas cancer including the addition of agents such as Bevacizumab (an anti VEGF-receptor monoclonal antibody) and Cetuximab to Gemcitabine have largely been negative[9]. In addition new immunotherapy targets have been identified in pancreatic cancer, which could lead to the development of novel therapies[10].

The paradigm of management for advanced pancreatic cancer changed further in October 2013 with the publication by Von Hoff et al.[10a] of the results of a randomized phase III study comparing the combination of nab-Paclitaxel and gemcitabine with the previous standard of single-agent gemcitabine, pre-FOLFIRINOX. A total of 861 patients were randomly assigned to nab-paclitaxel plus gemcitabine or gemcitabine alone. The median overall survival was 8.5 months in the nab-paclitaxel/gemcitabine group as compared with 6.7 months in the gemcitabine group (hazard ratio for death, 0.72; 95% confidence interval [CI], 0.62 to 0.83; 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 progression-free survival was 5.5 months in the nab-paclitaxel/gemcitabine group, as compared with 3.7 months in the gemcitabine group (hazard ratio for disease progression or death, 0.69; 95% CI, 0.58 to 0.82; P<0.001); the response rate according to independent review was 23% versus 7% in the two groups (P<0.001). There are currently no data for either gemcitabine/nab-Paclitaxel or FOLFIRINOX in the second-line setting. However a common extrapolation from both the first-line studies mentioned above has led many in the community to sequence FOLFIRINOX treatment followed upon disease progression by gemcitabine/nab-Paclitaxel for patients with advanced pancreatic cancer with good performance status.

1.2.2 NPC-1C

NPC-1C is a chimeric immunoglobulin molecule comprised from the variable region of the heavy chain and light chain of murine NPC-1, genetically engineered in-frame with the constant regions of a human IgG1 isotype. The recombinant protein originally manufactured for use in clinical studies was expressed in Chinese hamster ovary (CHO) cells and purified to homogeneity under GMP conditions by a contract manufacturer. This NPC-1C was referred to as NEO-101. Due to

diminishing supplies of NPC-1C (NEO-101) and with the intent to optimize the drug product and its stability, a new lot of NPC-1C was manufactured to replace NEO-101 for use in clinical studies. This lot, referred to as NEO-102, was manufactured by Cytovance Biologics, Inc. from a CHO-M clone 10-23 cell line. NEO-102 is the lot for use in this study. Extensive biocomparability studies were performed demonstrating that NEO-101 and NEO-102 are comparable antibody products with respect to purity, identity, strength and other physicochemical qualities.

The mature, secreted chimeric IgG has 4 subunits (2 heavy chains and 2 light chains) and has a predicted molecular mass of 152 kDa with a pI of 8.2. NPC-1 is a monoclonal antibody derived from a Tumor Associated Antigen (TAA) that was used in a TAA based vaccine previously tested in a Phase I-II clinical trial performed in the United States [11]. This Phase I study by Hollinshead et al. explored the use of TAA therapy in patients with adenocarcinoma of the colon [11]. The TAA was derived from pooled allogeneic colon cancer specimens from multiple patients, which was obtained post-operatively [12]. For the Phase I cancer vaccine trial, TAA was prepared from tumors of 78 selected hepatitis-free donors. Vaccines were prepared by mixing 0.2 mL TAA with 0.2 mL of complete Freund's adjuvant (CFA). Twenty-two patients received vaccinations with follow-up ranging from 3 months to 3 years (median 21 months). All patients underwent surgical resection, with six of eight patients with Dukes D clinically disease-free at the time of vaccination. Each patient received three monthly vaccinations. Two patients received 200 μg doses of TAA, two received 500 μg doses of TAA, and 18 received 300 μg doses. [13]. Although this was a small Phase I trial indicating the safety of the vaccine, at the median follow-up of 21 months, 82% of the patients were still alive, and 59% of the patients were without evidence of disease [11]. The murine monoclonal antibody NPC-1 was developed against an immunogenic TAA preparation from pooled allogeneic colon tumor tissue extracts. NPC-1 antibody was isotyped by testing culture medium collected from cells using isotyping strips (Amersham-Pharmacia) and by an ELISA-based isotyping kit (BD-Pharmingen). Results from both tests showed the mouse NPC-1 to express an IgG1 heavy chain and a Kappa light chain. The nucleotide sequence of the genes encoding NPC-1 heavy chain (HC) and light chain (LC) were determined. These sequences were found to be unique by BLAST database search and a patent was filed with the USPTO (US Patent 7,314,622, issued January 1, 2008). The DNA sequences encoding the heavy chain and light chain proteins were determined twice using RNA extractions made at different times. Both sequence determinations resulted in the identical DNA sequences, indicating that the sequences were reproducible and authentic. The mouse sequences represent the basis for designing the chimeric NPC-1 molecule. The murine NPC-1 antibody was genetically engineered to express the mouse variable regions (containing the CDRs) fused in-frame with human IgG1 constant regions. The resulting chimeric antibody was renamed NPC-1C and expressed in Chinese hamster ovary (CHO) cells, after which the 10-23 clone was selected for manufacturing the GMP-grade NPC-1C (NEO-102) drug product.

1.2.2.1 MUC5AC as the target antigen for NPC-1C

The target antigen for NPC-1C has been recently determined to be a protein with similarity to MUC5AC, a member of the mucin gene family. The MUC5AC gene has been reported to be expressed mainly in the surface epithelium of normal gastric mucosa [14] and normal airway epithelium [15]. Considered an oncofetal protein, MUC5AC is also expressed in the fetal and pre-cancerous colonic mucosa, but not in normal adult colon [16] [17]. The gene was also shown to be

overexpressed in inflammatory conditions such as Chronic Obstructive Pulmonary Disease [14] and H. Pylori infections of the GI tract. These conditions produce an excess mucus secretion associated with the abundantly glycosylated MUC5AC glycoprotein. Overexpression of MUC5AC has also been shown to be associated with pancreatic and colorectal cancer. However, it is believed that unlike the inflammatory conditions noted above where MUC5AC is heavily glycosylated, in pancreas and colon tumors MUC5AC was reported to be aberrantly glycosylated [18] [19] [20]., Antibody-staining results with NPC-1C demonstrated specific immunoreactivity with cancer tissues from colon and pancreas patients, whereas only weak binding, if at all, was observed in normal pancreas or colon tissues. Furthermore, no cross-reactivity was observed in other normal human tissues stained at Precision Biologics, Inc. indicating a strong positive correlation of the NPC-1C binding to colon and pancreas cancer tissues (Table 1). The immunohistochemical staining procedure has been developed into a highly reproducible, robust assay that will be used as part of this clinical trial. Eligibility will require that a prospective subject's tumor specimen stain with NPC-1C antibodies $\geq$ 20% in order to participate in the clinical trials.

Tissue Type	**% Positive NPC-1C (n)**
Pancreatic cancer	54% (n=126)
Normal pancreas	0% (n=14)
Colorectal cancer	53% (n=171)
Normal colon	27% (n=18)
Various normal	0% (n=115)

Table 1: Immunohistochemistry: Human Tissues With Biotinylated NPC-1C

1.2.2.2 *In vitro* data

The NPC-1C antibody was tested for antibody-dependent cell cytotoxicity (ADCC) activity against several colorectal and pancreatic tumor cell targets in vitro [21]. The data showed that in a standard 4-hour 111-Indium release assay that NPC-1C facilitates the killing of the colorectal and pancreatic tumor cell lines that express the NPC-1C epitope on the MUC5AC-like target antigen, but does not react towards melanoma or prostate specificity control cell lines. These *in vitro* results demonstrate that the NPC-1C antibody is capable of directing antibody-dependent cell cytotoxicity in the presence of normal human PBMCs (Table 2). The data also justified further pre-clinical testing of the NPC-1C candidate in anti-tumor efficacy studies using pre-established xenograft tumors in nude mice.

Tumor Cell Line Target	Effector:Target Cell Ratio	% Specific Killing (± SEM)	
		Isotype control Ab	NPC-1C
Colo-205 (Colorectal)	50:1	9.8 ± 1.9	66.7 ± 0.6
	25:1	0.8 ± 1.2	46.4 ± 1.6
	12.5:1	-0.5 ± 0.1	32.8 ± 2.0
SW620 (Colorectal)	50:1	1.6 ± 0.2	63.7 ± 2.9
	25:1	3.5 ± 1.8	61.0 ± 1.8
	12.5:1	0.0 ± 0.3	51.5 ± 0.9
SW1463 (Colorectal)	50:1	0.1 ± 1.1	33.8 ± 1.0
	25:1	-1.3 ± 0.2	25.5 ± 0.6
	12.5:1	-1.2 ± 0.1	17.9 ± 1.7
LS174T (Colorectal)	50:1	-1.2 ± 0.1	26.8 ± 2.9
	25:1	-0.8 ± 0.1	18.5 ± 4.1
	12.5:1	-1.1 ± 0.0	9.5 ± 0.5
AsPC-1 (Pancreatic)	50:1	-0.8 ± 2.9	44.5 ± 6.8
	25:1	-7.0 ± 2.2	36.2 ± 2.6
	12.5:1	-1.2 ± 0.9	26.5 ± 6.7
CFPAC-1 (Pancreatic)	50:1	-1.2 ± 2.3	26.9 ± 1.6
	25:1	-2.4 ± 0.1	23.2 ± 2.2
	12.5:1	-2.0 ± 0.4	11.1 ± 1.6
PANC-1 (Pancreatic)	50:1	-2.2 ± 0.4	46.8 ± 2.1
	25:1	-2.5 ± 0.4	33.2 ± 3.3
	12.5:1	-3.9 ± 0.3	21.2 ± 0.6
SK-MEL (Melanoma)	50:1	2.7 ± 0.7	4.6 ± 1.1
	25:1	1.5 ± 0.3	3.3 ± 1.1
	12.5:1	1.6 ± 0.4	2.3 ± 0.6
DU145 (Prostate)	50:1	-0.3 ± 0.2	-0.5 ± 0.3
	25:1	-0.7 ± 0.1	0.3 ± 0.8
	12.5:1	-0.2 ± 0.2	-0.3 ± 0.1

Table 2: ADCC Assay: NPC-1C Killing Against Tumor Cell Lines

1.2.2.3 Pre-clinical data for NPC-1C efficacy

The NPC-1C was tested for anti-tumor efficacy using the human AsPC-1 pancreas tumor xenograft model in nude mice. In this efficacy model, mice were implanted with human AsPC-1 tumor cells and allowed to establish to approximately 20-50 mm^3, in approximately 4-6 days. The treatment phase included intraperitoneal injection of 200 ug (10mg/kg) of research-grade NPC-1C or a negative control human IgG, followed on the next day with an intraperitoneal injection of IL-2-activated normal human PBMCs (approximately $2x10^7$ per mouse per injection). Four cycles of

treatment were administered. As shown in Figure 1, tumor inhibition was evident during the treatment phase of the study, and the difference between the NPC-1C treated mice and the human IgG control mice was statistically significant beginning on Day 18 and continuing for the remainder of the study with P=0.0044 by one-way ANOVA (n=8 per group) (Figure 1: NPC-1C Anti-Tumor Efficacy, (AsPC-1 Model)).

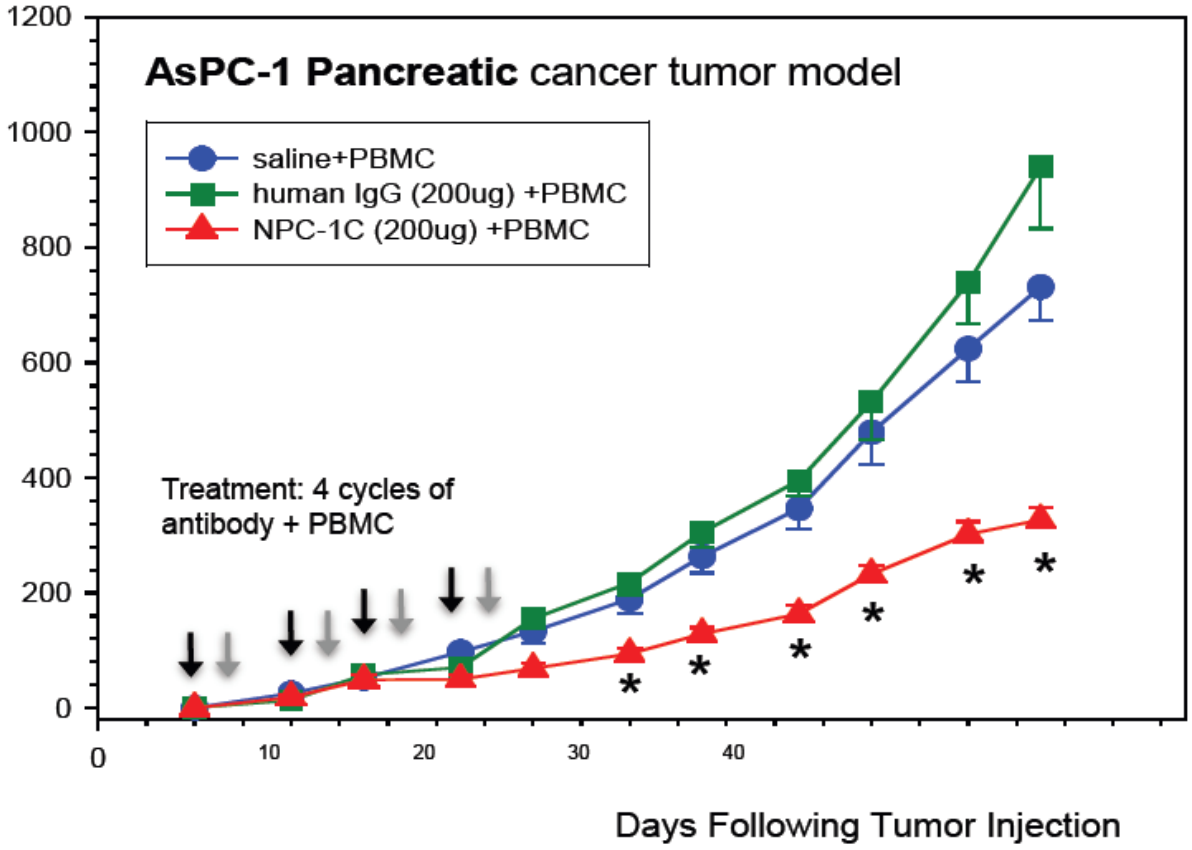


Figure 1: NPC-1C Anti-Tumor Efficacy, (AsPC-1 Model)

Dark arrows indicate days of NPC-1C injection (ip), gray arrows indicate days of PBMC injection (ip), the asterisk (*) indicates statistically significant differences between NPC-1C treated mice with human IgG treated mice.

1.2.3 The rationale of combining NPC-1C (NEO-102) with Gemcitabine

Increasing evidence has been mounting to suggest that immunotherapy has the possibility of achieving better success when used in combination with conventional chemotherapy [22, 23]. A standard cytotoxic agent, Gemcitabine, not only exerts direct antitumor activity, but also mediates immunological effects relevant for cancer immunotherapy [24] [25] [26]. Cross-presentation of TAAs by DCs is essential for induction of augment CTL responses. Treatment of cancer cells and DCs with gemcitabine results in enhanced cross-presentation of TAAs by DCs, CTL expansion, and infiltration of the tumor, all of which are associated with augmented CTL [27] [28] [29] [30]. The increase in cross-presentation did not lead to tolerance [27] [28]. Moreover, Gemcitabine

reduced the number of myeloid suppressor cells but did not reduce CD4+ T cells, CD8+ T cells, NK cells, macrophages, or B cells [31, 32] [33]. Therefore, the addition of NPC-1C (NEO-102) to Gemcitabine may enhance its immune effect presumably by enhancing the antibody-dependent cell cytotoxicity (ADCC) activity against pancreatic cancer cells.

Since Gemcitabine is the standard of care for patients who progress on FOLFIRINOX and its immune efficacy could be enhanced by NPC-1C (NEO-102) antibody these two agents will be combined in this study.

1.2.3.1 Pre-clinical data in support of NPC-1C (NEO-102) in combination with Gemcitabine

A growth and response curve was conducted using a xenograft model using the pancreatic cancer cell line ASPC1 to determine the suitability as a model and the growth response to Gemcitabine with both 60mg/kg and 100mg/kg in preparation for the combination studies with NPC-1C antibody. Both 60mg/kg and 100mg/kg of Gemcitabine were relevant doses, which gave partial responses for tumor growth admission. A study using the ASPC1 xenograft pancreatic cell line that expresses the antigen recognized by NPC-1C was conducted. In this study NPC-1C was combined with Gemcitabine to determine any additive or synergistic activities. Gemcitabine was given on day 1, 8 and 15 followed by NPC-1C on day 3, 10 and 17. Human PBMC were given on day 4, 11 and 18. NPC-1C and Gemcitabine did not interfere with the others activity, and no additional toxicity was identified. Interestingly the groups treated with the combination of NPC-1C and 60mg/kg Gemcitabine had 3 out of 10 animals terminated on study because of ulcerated tumors, suggesting a potential active immunological response at the tumor site (Precision Biologics, unpublished data). The fact that this study showed that the combination of NPC-1C and Gemcitabine had no negative impact on the Gemcitabine's efficacy, but if at all it might have a potential positive effect, supports the rationale to use this combination in a clinical trial.

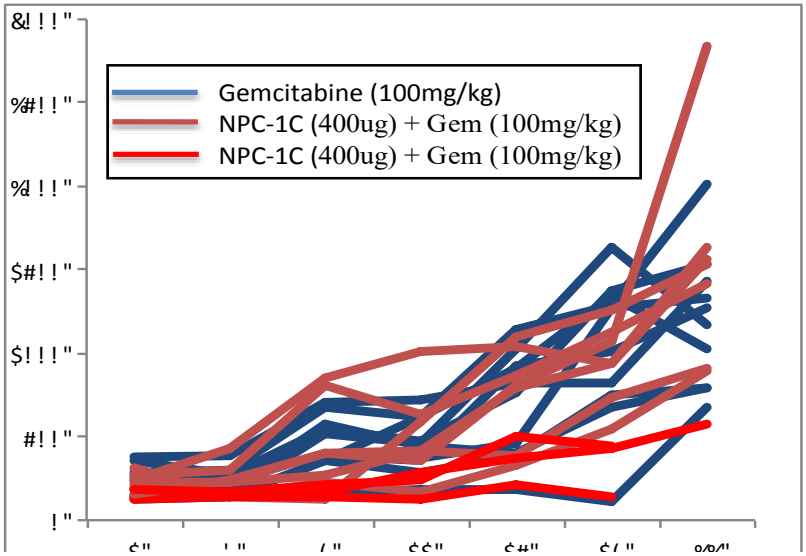


Figure 2: NPC-1C antibodies + Gemcitabine Anti-Tumor Efficacy, (AsPC-1 Model)

Tumor volume measured on Day 1-Day 22. Blues lines indicate mice treated with Gemcitabine alone, bordeaux/red lines indicate mice treated with Gemcitabine + NPC-1C. Red lines indicate mice with tumor necrosis.

1.2.4 Clinical experience with NPC-1C

1.2.4.1 NPC-1C Monotherapy in patients with advanced pancreatic and colorectal cancer

A Phase I/IIA open label, multi-center dose escalation clinical trial with NPC-1C(NEO101) antibody was conducted in patients with advanced pancreatic and colorectal cancer who are refractory to standard therapy [34]. In February 2013, NEO-102 a glycoengineered reformulation of NEO101 for improved stability and reduced RBC agglutination, was given approval by FDA for use in clinical trials. A dose escalation monotherapy study has been performed with NEO-102. The primary objective of this study was to determine the safety and tolerability of escalating doses of NEO-102 monoclonal antibody in patients with advanced, recurrent or metastatic pancreatic or colorectal cancer. Patients were selected based upon immunohistochemistry (IHC) testing for NPC-1 antigen expression. For this purpose, archival paraffin embedded tissue was tested and a minimum of 20% of tissue staining positive at ≥ 2 + intensity was required for eligibility. Three to six patients were treated at each dose level, 1.5 mg/kg, 2 mg/kg, 3 mg/kg and 4 mg/kg. NEO-102 was administered intravenously (IV) on days 1, 15, 29 and 43 of a 57 day cycle. Premedication with dexamethasone (10mg IV), ranitidine (50mg IV) and diphenhydramine (25-50 mg IV) was administered prior to each dose. Additional courses could be offered in the absence of dose limiting or unacceptable toxicity, progressive disease, or per patient/investigator discretion.

A total of 19 patients (4 pancreatic and 15 colon cancer) received at least one dose of NEO-102 in the Phase I portion of this study at participating institutions. Median age was 57 years (range 32-69), 58% (11 patients) were male, median number of prior treatment regimens was 3 (range 1+ to 8). Preplanned dose escalation to the 4 mg/kg dose was completed and no dose limiting toxicity was observed in the first 3 patients. The sixth and seventh patients receiving 4 mg/kg of NEO-102 experienced dose limiting toxicities, grade 3 anemia and transient asymptomatic grade 3 hyperbilirubinemia, respectively. The fifth patient at this dose experienced a transient asymptomatic grade 3 hyperbilirubinemia after the 3rd dose of NEO-102 in the first course of therapy. Although these events occurred after completion of dose escalation, a decision to de-escalate to 3 mg/kg was made to ensure safety of subsequent patients enrolled. Three additional patients were then treated at the 3 mg/kg dose level with 1 out of 6 patients experiencing DLT (grade 3 reversible hypoxia, possibly related). Hence 3 mg/kg was established as the maximum tolerated dose (MTD).

This study was subsequently expanded to include two arms for analysis of overall survival: patients with metastatic colorectal cancer and patients with metastatic, locally advanced unresectable or recurrent pancreatic cancer.

Analysis of the patients in the colorectal cancer arm: Fifty-four (54) patients were enrolled, one (1) withdrew prior to the first dose; 53 patients received ≥ 1 dose of NEO-102 and were eligible for toxicity evaluation. Grade 3 and 4 suspected adverse events (AEs) (reported as # events /total # of doses [227 doses]): anemia (1.3%), hyperbilirubinemia (0.9%), fatigue (0.9%), and hemolysis, nausea, vomiting, headache, hypoxia (0.4%). The most common grade 1-2 suspected AEs were anemia, fatigue, nausea, vomiting, flushing, hyperbilirubinemia, constipation, diarrhea, hemolysis, and dyspnea, chills. Other toxicities reported in 1 patient each included platelet count decrease, neutrophil decrease, AST increase, rash, hypoesthesia, malaise, gait

disturbance, mucosal inflammation, pharyngeal edema, upper airway cough syndrome, hypertension, hypokalemia, B-12 deficiency, back pain, myalgia, creatinine increase, chromaturia, night sweats.

Forty-eight (48) patients received ≥ 2 doses and were evaluable for the primary endpoint (OS); 41 patients were evaluated for RECIST response. Nine (9) patients were taken off treatment for other reasons, i.e. patient decision, investigator decision, and prolonged intercurrent illness. Only two patients were removed for treatment-related toxicity: 1 for prolonged anemia, and 1 for grade 3 hypoxia. Despite advanced disease in this population, amongst patients evaluated by RECIST, 9/41 (22%) exhibited overall stable disease (SD) at the end of the first course (D57). Survival of subjects with CRC participating in the Phase 1 (15 subjects) and Phase 2 (48 subjects) portions of this monotherapy study receiving at least two doses of NEO-102 was 6.9 months; similar to the OS observed in subjects in the Phase 2 portion alone who received NEO-102 at 3 mg/kg (6.6 months), with the longest survival of 30.2 months.

Analysis of the patients in the pancreatic cancer arm: Thirty-seven (37) patients were enrolled in the arm with pancreatic cancer, three (3) patients withdrew prior to the first dose; 1 patient withdrew during the first infusion due to investigator discretion, 33 patients received ≥ 1 dose of NEO-102 and were eligible for toxicity evaluation. Grade 3 and 4 suspected adverse events (AEs) (reported as # events /total # of doses [90 doses]): anemia (5.6%), fatigue (2.2%), hemolysis (1.1%), and hyperbilirubinemia (1.1%). The most common grade 1 / 2 toxicities were anemia (21.1%), fatigue (14.4%), hemolysis (7.8%), nausea (6.7%), d-dimer increase, hyperbilirubinemia, decreased appetite, and asthenia (4.4%), allergic reaction (3.3%), LDH increase, chills, vomiting and diarrhea (2.2%). The following toxicities each occurred in 1 patient: decreased ALC, increase thrombin time, decreased reticulocytes, decreased haptoglobin, thrombocytopenia, ALP, ALT and AST increased, flushing, weight loss, edema, constipation, abdominal pain, dyspepsia, mucosal inflammation, dysgeusia, upper airway cough, hypertension, bradycardia, back pain, musculoskeletal pain, bruising and pruritus

Twenty-four (24) patients were evaluable for response (received ≥ 2 doses of NEO-102). Of these 24 patients, the average number of prior therapies was 3.3 (range 2-6), doses of NEO-102 ranged from 2 to 16 doses (median = 4). Fifteen (15) patients received 4 or more doses and were evaluable for response; two were taken off study for clinical progression without completing tumor measurements, 3 patients had stable disease (SD) by RECIST after 8 weeks. Ten (10) patients were removed from therapy prior to completing a full course (with evaluation at D57). One (1) patient chose with withdraw after two doses, 2 patients were removed from therapy for treatment-related toxicity (anemia) and 10 stopped treatment for disease progression. Median overall survival is 2.4 months (range 1-11.9+) with 3 patients still alive (as of 5-16-16).

1.2.5 Rationale for selection of study population, treatment dose and schedule

1.2.5.1 Rationale for selection of study population

Patients with metastatic or locally advanced pancreatic cancer are currently being treated with the traditionally used Gemcitabine-based chemotherapy or the newly developed FOLFIRINOX

chemo regimen in the first line setting based on the Conroy et al study [6]. Patients who progressed on FOLFIRINOX had a median OS of 4.4 months when they received Gemcitabine as a second line treatment. Our proposed study population will be similar to that treated with second line Gemcitabine in the Conroy et al study, as it will require patients to have received FOLFIRINOX as a first line treatment. This would give a reasonably comparable historical control of median OS (4.4 months) in the second line setting.

1.2.6 Status of Protocol and rationale for amendment F (February 2014)

This protocol was originally designed as a single-arm study evaluating the combination of Gemcitabine and NPC-1C (NEO-102) as a second line therapy in subjects with metastatic, locally advanced unresectable or recurrent pancreatic cancer previously treated with FOLFIRINOX or a FOLFIRINOX-like regimen. Three subjects were enrolled and received NPC-1C 1.5 mg/kg on Days 1 and 15, with Gemcitabine 1000 mg/m^2 on Days 1, 8 and 15 for a 28 day cycle. All three subjects completed the 28 day toxicity evaluation without DLT. Toxicities observed included: anemia (grade 3) possibly related to NPC-1C; fatigue (grade 3), hyperglycemia (grade 3) and anorexia (grade 3) unlikely related to NPC-1C; anemia (grade 3), thrombocytopenia (grade 4) unlikely related to NPC-1C and likely related to gemcitabine. Hence, the NPC-1C dose established for the Phase 2 component of this study was 1.5 mg/kg for subsequent subject enrollment. Although the monotherapy trial determined the MTD to be 3 mg/kg, the decision was made to maintain the dose of NEO-102 at 1.5 mg/kg to ensure safety of the combined regimen. Two additional patients were enrolled and treated in the Phase 2 component with the combination of Gemcitabine and NPC-1C/NEO-102. The first patient completed six cycles of therapy and achieved stable disease post cycle 2 and post cycle 4. The second patient received five cycles of therapy with stable disease after cycles 2 and 4. All toxicities were mild (grade 1 or 2) with the exception of one episode of grade 3 neutropenia possibly related to study drug, probably related to gemcitabine. Toxicities (grade 1 or 2) included nausea, vomiting, constipation, difficulty breathing, fatigue, anxiety, mucositis and night sweats. No serious adverse events occurred in the additional patients enrolled receiving NEO-102 in combination with gemcitabine.

Following publication of the phase III gemcitabine/nab-paclitaxel data and FDA approval of this regimen, screening and enrollment to 13-C-0009 at the participating sites declined significantly. This was thought to reflect the altered therapeutic paradigm in pancreatic cancer whereby patients with good performance status are treated initially with FOLFIRINOX followed upon disease progression by gemcitabine/nab-paclitaxel despite the lack of supportive data for the latter regimen in the second line setting. It was decided to amend the study (amendment F) to evaluate NPC-1C in combination with the gemcitabine/nab-paclitaxel regimen that is now widely used. Because the original single-arm study was being benchmarked against historical gemcitabine-alone controls and because there are no data for gemcitabine/nab-paclitaxel regimen in the second-line setting, amendment G will contain a control arm of gemcitabine/nab-paclitaxel alone.

Status of Randomized Phase II Study to Date (May 1, 2015): In the current design, eligible patients will be randomized to either Arm A: Gemcitabine (1000 mg/m^2 IV) with nab-Paclitaxel

(125 mg/m^2 IV) on days 1, 8, and 15 with NEO-102 (1.5 mg/kg) IV on days 1 and 15 of a 28-day cycle, or to Arm B: Gemcitabine (1000 mg/m^2 IV) with nab-Paclitaxel (125 mg/m^2 IV) on days 1, 8, and 15 of a 28 day cycle. Six patients have been randomized on this trial since it was approved by the FDA in spring 2014. Three patients to each arm. One patient randomized to Arm B withdrew upon randomization and did not receive any treatment on this study. One patient on Arm A experienced an unrelated serious adverse event after the first dose and was taken off study, deemed not-evaluable. At this time there are two patients evaluable in Arm A and one patient evaluable in Arm B (the other patient in Arm B is too early to evaluate).Toxicities have been mild (grades 1/2), anemia, hypoalbuminemia, fatigue, anorexia, weight loss, body rash, pruritus, fever, mucositis. Additional toxicities probably related to the chemotherapy regimen but possibly related to NEO-102 include thrombocytopenia, neutropenia, and lymphocytopenia. The safety profile to date is acceptable. Additional sites are being recruited to enhance enrollment on this study.

2 ELIGIBILITY ASSESSMENT AND ENROLLMENT

2.1 ELIGIBILITY CRITERIA

2.1.1 Inclusion Criteria

2.1.1.1 Subjects with measurable recurrent, locally advanced unresectable or metastatic adenocarcinoma of the pancreas who have progressed after primary therapy; must have progressed after FOLFIRINOX or FOLFIRINOX-like regimen or were intolerant of it (including if administered in adjuvant setting). FOLFIRINOX regimen is defined as follows: oxaliplatin, 85 mg/m^2; irinotecan, 180 mg/m^2; leucovorin, 400 mg mg/m^2; and fluorouracil, 400 mg/m^2 given as a bolus followed by 2400 mg/m^2 given as a 46-hour continuous infusion, every 2 weeks. FOLFIRINOX –like regimen could consist of 5-FU/leucovorin or capecitabine, combined with either irinotecan, oxaliplatin or both. FOLFIRINOX intolerance is defined as inability to tolerate the FOLFIRINOX regimen due to side effects and or toxicities determined by the treating medical oncologist.

The histology of the primary tumor should be confirmed at NCI or the other participating sites.

2.1.1.2 IHC: ≥ 20% of tumor on tissue sections must stain with NPC-1C.

2.1.1.3 Age: ≥ 18 years of age.

2.1.1.4 Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1 (Appendix A).

2.1.1.5 Have an anticipated life expectancy of greater than 8 weeks.

2.1.1.6 Patients must have recovered from any acute toxicity related to prior therapy. Toxicity should be ≤ grade 1 or ≤ grade 2 for peripheral neuropathy, or returned to baseline.

2.1.1.7 If female, is post-menopausal, surgically sterilized or willing to use an effective method of contraception (i.e., a hormonal contraceptive, intra-uterine device, diaphragm with spermicide, or condom with spermicide, or abstinence) for the duration of the study and

for 3 months after the end of treatment. If male, has agreed to use barrier method for contraception for the duration of the study and for 3 months after the end of treatment.

2.1.1.8 Patient must be willing to sign a written informed consent

2.1.1.9 Laboratory tests meet minimum safety requirements:

- Hemoglobin ≥ 8.5 g/dL (may be receiving supportive therapy)
- ANC ≥ 1,500/uL
- Platelets ≥ 100 K/uL
- Total bilirubin ≤ 2 mg/dL
- ALT/AST ≤ 3 times ULN or ≤ 5 times ULN in the setting of liver metastases
- Creatinine ≤ 1.5 mg/dL or creatinine clearance (Cl_{cr}) > 40 mL/min/1.73 m^2 for patients with creatinine levels above institutional normal, a[s] calculated by the Cockcroft Gault formula and weighted by body surface area; i.e.:

$$Cl_{cr}\ (\text{females}) = = \frac{(140 - \text{age}) \times \text{ABW}}{\text{SCr} \times 72} \times 0.85 \times \frac{1.73\ m^2}{\text{pt's BSA } (m^2)}$$

$$Cl_{cr}\ (\text{males}) = = \frac{(140 - \text{age}) \times \text{ABW}}{\text{SCr} \times 72} \times \frac{1.73\ m^2}{\text{pt's BSA } (m^2)}$$

ABW, actual body weight; BSA, body surface area

2.1.2 Exclusion Criteria

2.1.2.1 Patients who received second line chemotherapy after progressing on or not tolerating treatment with FOLFIRINOX. Prior adjuvant/neoadjuvant gemcitabine or gemcitabine-based radiation will not be counted as first line therapy.

2.1.2.2 Patients with known brain metastases should be excluded from this clinical trial because of their poor prognosis and because they often develop progressive neurologic dysfunction that would confound the evaluation of neurologic and other adverse events.

2.1.2.3 Any major surgery within four weeks before enrollment.

2.1.2.4 Greater than grade 2 ascites at time of enrollment.

2.1.2.5 Patients who:

- Received Gemcitabine for palliative treatment; or
- Received Gemcitabine for recurrent or metastatic disease; or
- Is within 3 months of receiving Gemcitabine in the adjuvant/neo-adjuvant setting.

2.1.2.6 Uncontrolled concomitant illness including, but not limited to, ongoing or active infection, symptomatic congestive heart failure, unstable angina pectoris, or cardiac arrhythmia.

2.1.2.7 Serious medical or psychiatric illness, that could, in the Investigator's opinion, potentially interferes with the completion of treatment according to this protocol.

2.1.2.8 Patients must not have other invasive malignancies within the past 3 years (with the exception of non-melanoma skin cancers or non-invasive bladder cancer).

2.1.2.9 Pregnant or breast-feeding

Since the effects of NPC-1C on the developing human fetus and nursing infants are unknown and potentially harmful, women of child-bearing potential must agree to use adequate contraception (hormonal or double barrier method of birth control or complete abstinence) prior to study entry, for the duration of study participation, and for three months after the last dose of investigational agent. Should a woman become pregnant or suspect she is pregnant while participating in this study, she should inform her treating physician immediately.

2.1.2.10 Any chemotherapy, or systemic corticosteroids within 2 weeks before study entry.

2.1.2.11 Patients who have acquired, hereditary, or congenital immunodeficiencies including cellular immunodeficiencies, hypogammaglobulinemia and dysgammaglobulinemia.

2.1.2.12 Prior history of a documented hemolytic event.

2.1.2.13 History of hypersensitivity to human or mouse antibody products.

2.1.2.14 Patients with a known history of HIV are excluded due to the possibility that Gemcitabine/nab-paclitaxel or NPC-1C(NEO-102) may worsen their condition and the likelihood that the underlying condition may obscure the attribution of adverse events with respect to Gemcitabine/nab-paclitaxel or NPC-1C(NEO-102).

2.1.3 Inclusion of Women and Minorities

Men and women of all races and ethnic groups are eligible for this trial.

2.2 SCREENING EVALUATION

Prospective subjects will be screened for inclusion in the study in two phases: IHC screening and Study Screening. According to procedures determined by each clinical study site's IRB, informed consent for both screenings may be obtained with either one document or with two separate documents.

2.2.1 IHC Screening Phase

IHC staining of the tumor on tissue sections with NPC-1C may be obtained at any time prior to further eligibility screening for this study. Subjects who sign the IHC Screening informed consent document will be entered on the IHC Screening Log sheet. IHC Screening informed consent may be obtained via phone consent according to institutional IRB policy. The IHC will be performed and interpreted at UT Southwestern Medical Center CLIA certified central lab (see Section 5.1).

2.2.2 Study Screening Phase

If IHC demonstrates tissue stain ≧ 20% positive for NPC-1C antibody/antigen target, subjects will be required to sign the Protocol Informed Consent document and will be entered on the Study Screening Log Sheet and proceed to undergo a complete eligibility evaluation.

2.2.2.1 History and physical exam with vital signs, body weight and height (obtained within 21 days prior to enrollment).

2.2.2.2 Laboratory evaluation (obtained within 21 days prior to enrollment)

- Hematological profile: CBC with differential and platelet count, PT, aPTT, fibrinogen.
- Biochemical profile: electrolytes, BUN, creatinine, AST, ALT, ALP, total bilirubin, calcium, phosphorus, albumin, magnesium, uric acid, albumin, and lactate dehydrogenase (LDH).
- Pregnancy test for women of childbearing potential.

2.2.2.3 Imaging studies (obtained within 28 days prior to enrollment):

- CT scan of chest, abdomen and pelvis
- MRI if unable to obtain CT scan

2.2.2.4 Electrocardiogram (obtained within 28 days prior to enrollment).

2.3 REGISTRATION PROCEDURES

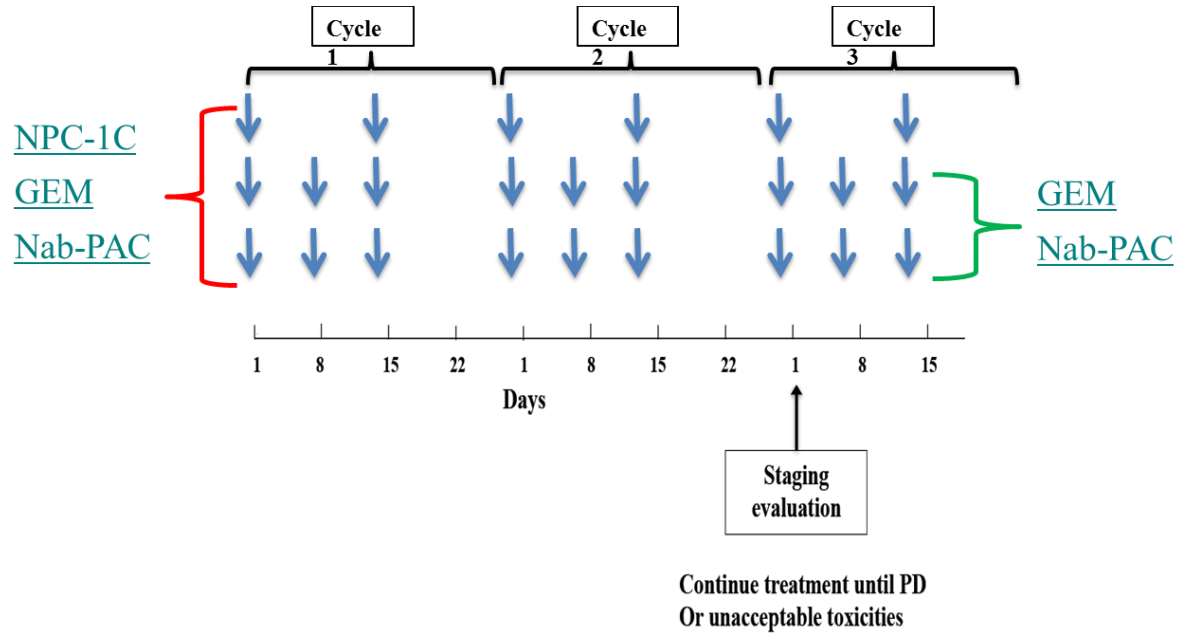
Subjects at all of the participating sites who are evaluated and determined to be eligible will have Eligibility Checklist completed (Appendix C, or comparable study site registration form) according to source documentation, and e-mailed (preferred) or faxed to the Medical Advisor (Phil Arlen, M.D.) of the Sponsor at: cell phone: 301-728-4883; Fax: 240-669-9828; or e-mail parlen@Precision-Biologics.com, with email cc'd to azaki@Precision-Biologics.com, kcui@Precision-Biologics.com, smavroukakis@Precision-Biologics.com, prior to initiation of treatment with study drug. Subjects will be identified only by the subject initials. Once the Sponsor Medical Advisor reviews and approves eligibility (by e-mail or fax) the Sponsor submits the eligibility form to the NCI Central Registration Office where the randomization # and the subject identification number will be assigned. This information is returned to the Sponsor who provides approval to the site for the subject to proceed to treatment.

3 STUDY IMPLEMENTATION

3.1 STUDY DESIGN

This is a randomized phase II multi-institution prospective open label study in which up to 94 subjects with measurable, metastatic, locally advanced unresectable or recurrent pancreatic cancer who failed or did not tolerate chemotherapy with FOLFIRINOX or a FOLFIRINOX-like regimen will be enrolled into one of two arms, A or B. Ninety evaluable patients can be treated on this trial; in order to allow for a very small number of inevaluable patients, the accrual ceiling will be set at 94 patients.

Study Design and Drug Administration
Arm A and Arm B



3.2 TREATMENT PLAN

Patients will be randomized between Arms A and B, i.e. the combination of gemcitabine and nab-paclitaxel with or without the addition of the experimental agent NPC-1C (NEO-102) respectively. Because NPC-1C (NEO-102) has been established to be safe when given with gemcitabine alone but not the combination of gemcitabine and nab-paclitaxel, stopping rules for safety will be adhered to for the first N=6 patients randomized to Arm A.

3.2.1 Treatment Dose and Schedule

Arm*	**Gemcitabine (mg/m^2 IV on days 1, 8, and 15 of a 28-day cycle)**	**Nab-paclitaxel (mg/m^2 IV on days 1, 8, and 15 of a 28-day cycle)**	**NPC-1C** (NEO-102) **(mg/kg IV every other week on days 1 and 15 of a 28-day cycle)**
A	1000	125	1.5
B	1000	125	No NPC-1C
*Patients will be randomized between Arms A and B.			

Table 3: Schedule

All patients will receive nab-paclitaxel followed by gemcitabine. Nab-paclitaxel will be administered at a dose of 125 mg/m2 as a 30 minute infusion (maximum infusion time not to exceed 40 minutes) followed by 1000 mg/m2 gemcitabine as a 30 minute infusion for 3 consecutive weeks followed by a week of rest (treatment on days 1, 8, and 15, during a 28-day cycle for both treatment arms A and B).

Patients on arm A will receive NPC-1C (NEO-102) infusion at a dose of 1.5mg/kg IV on days 1 and 15 of a 4-week cycle. This will be administered 30 minutes after completion of the gemcitabine infusion.

Gemcitabine, nab-paclitaxel and NPC-1C (NEO-102) doses will be calculated using weight or body surface area (BSA) based on the height and weight obtained during screening, unless body weight on Day 1 of a cycle increases or decreases greater than 10% from the weight measured during screening. If body weight changes >±10% from the screening weight measurement, obtained before cycle 1, doses will be recalculated based on the weight measured on Day 1 of repeated treatment cycles.

Three patients will be tested at dose level 1 (NPC-1C (NEO-102) 1.5 mg/kg) and if 0/3 or 1/3 has a DLT, then three more will be enrolled at this level; if 0-1 of 6 has a DLT, this will be the dose used in the expansion phase. If 2+/6 has a DLT at 1.5 mg/kg, then the next cohort of 3 patients will be enrolled at dose level -1 (1.0 mg/kg). If 0/3 or 1/3 has a DLT, then 3 additional patients will be enrolled at this level; if 0-1 of 6 has a DLT at 1.0 mg/kg, then the expansion cohort will be conducted using 1.0 mg/kg. If 2-3 patients in the first 3 treated at 1.0 mg/kg have a DLT, or 2+/6 at 1.0 mg/kg have a DLT then the study will stop accrual. COMPLETED.

3.3 DOSE LIMITING TOXICITY- COMPLETED

3.3.1 Definition of Dose-limiting Toxicities (DLTs):

3.3.1.1 Dose limiting toxicity

- Grade 3 or higher non-hematological toxicity considered related to the combination of NPC-1C (NEO-102) and Gemcitabine will be defined as a DLT.
- Grade 4 hematologic toxicities due to NPC-1C (NEO-102) or the combination therapy that does not resolve to ≤ grade 2 after appropriate treatment with filgrastim, or blood transfusion within 14 days after holding the treatment. Toxicities related to Gemcitabine alone will be treated according to modifications specified in section 3.5.1.
- Any grade 3 or higher hematological or non-hematological toxicity considered related to (possibly, probably or definitely) NPC-1C (NEO-102), except transient known toxicity related to NPC-1C (NEO-102) infusion including fatigue, local reactions, flu-like symptoms, fever, and headache. To be considered a DLT exception, these toxicities must recover to grade 1 or less within 8 hours after standard supportive treatment.

3.3.1.3 Exclusions to Dose Limiting Toxicities- COMPLETED

- Grade 3 electrolyte toxicities that can be corrected to Grade 1 or less within 24 hours will not be considered dose limiting.
- Grade 3 hypertension that can be controlled with oral medications and does not require treatment delay for > 7 days will not be considered a DLT.
- Grade 3 diarrhea will only be considered dose-limiting if it is refractory to anti-diarrhea medications and unable to be corrected to Grade 1 or less within 48 hours.
- Grade 3 nausea and vomiting will only be considered dose-limiting if it is refractory to anti-emetic therapy and unable to be corrected to Grade 1 or less within 48 hours.
- Grade 3 rise in creatinine, not corrected to Grade 2 or less after 2 liters of intravenous fluids within 24 hours, will be considered dose limiting.
- Grade 3 elevation in AST/ALT will only be considered dose limiting if they are also ≥ 1.5 times the baseline level. (This is because patients who have liver metastases with Grade 2 transaminase levels are eligible for study entry).
- Grade 3 elevation on ALP (Alkaline phosphatase) will not be considered a DLT.
- Grade 3 hypoalbuminemia will not be considered a DLT.
- Grade 3 lymphopenia will not be considered a DLT.
- Grade 3 rash will not be considered dose limiting unless it does not return to ≤ Grade 2 after 1 week of symptomatic treatment.

Three patients must complete at least 1 cycle of therapy (Day 28 of Cycle 1) prior to considering treating 3 more patients on the same dose level or on the next dose level. Accordingly, no more patients will be treated until at least three patients have completed the first cycle. Determination of DLT for the purpose of dose de-escalation enrollment will be based on toxicities observed in the first 28 days of treatment (cycle 1) and must be considered at least possibly related to NPC-1C(NEO-102) or the combination of NPC-1C(NEO-102) and Gemcitabine. Since the attribution of toxicities between the two drugs is difficult to determine, the investigator discretion is permitted to determine which drug is the source for a given toxicity.

3.4 STOPPING RULES FOR SAFETY OF ARM A

3.4.1.1 Stopping rules:

If ≥2 of the first 6 patients on Arm A experience any one of the following, enrollment will be suspended pending IRB and FDA consultation on how to proceed:

- Grade 3 or higher non-hematological toxicity considered related to the addition of NPC-1C(NEO-102) to the Gemcitabine/nab-Paclitaxel combination will be defined as a DLT with the exception of all expected toxicities clearly attributed to the Gemcitabine/nab-paclitaxel combination. If not considered to be related to the addition of NPC-1C (NEO-102) then refer to dose modifications as per Section 3.6.

- Grade 4 hematologic toxicities due to NPC-1C (NEO-102) or the combination therapy that does not resolve to grade ≤2 after appropriate treatment with filgrastim, or blood transfusion within 14 days after holding the treatment.
- Grade 2 or greater hemolysis as defined in Section 3.4.1.3.

3.4.1.2 Exclusions to stopping rules:

- Grade 3 electrolyte toxicities that can be corrected to Grade 1 or less within 24 hours will not be considered dose limiting.
- Grade 3 hypertension that can be controlled with oral medications and does not require treatment delay for > 7 days will not be considered a DLT.
- Grade 3 diarrhea will only be considered dose-limiting if it is refractory to anti-diarrhea medications and unable to be corrected to Grade 1 or less within 48 hours.
- Grade 3 nausea and vomiting will only be considered dose-limiting if it is refractory to anti-emetic therapy and unable to be corrected to Grade 1 or less within 48 hours.
- Grade 3 rise in creatinine, not corrected to Grade 2 or less after 2 liters of intravenous fluids within 24 hours, will be considered dose limiting.
- Grade 3 elevation in AST/ALT will only be considered dose limiting if they are also ≥ 1.5 times the baseline level. (This is because patients who have liver metastases with Grade 2 transaminase levels are eligible for study entry).
- Grade 3 elevation on ALP (Alkaline phosphatase) will not be considered a DLT.
- Grade 3 hypoalbuminemia will not be considered a DLT.
- Grade 3 lymphopenia will not be considered a DLT.
- Grade 3 rash will not be considered dose limiting unless it does not return to ≤ Grade 2 after 1 week of symptomatic treatment.

3.4.1.3 Hemolysis Evaluation

If hemoglobin drops greater than 1gm/dL then an evaluation should be performed for evidence of hemolysis, which may include direct antiglobulin test (DAT) (also known as direct Coomb's test), schistocytes smear, serum haptoglobin and/or urinalysis.

In addition to the definition in CTCAEv4.0, **hemolysis** will be graded using the following expanded guideline:

- Grade 1: Laboratory evidence of hemolysis with no increase in creatinine serum levels above normal limits.
- Grade 2: Laboratory evidence of hemolysis of a grade 2 or Any hemolysis with Grade 1 creatinine elevation
- Grade 3: One of the following:
  - Any laboratory evidence of hemolysis and Grade 2 creatinine elevation
  - Any laboratory evidence of hemolysis and Grade 3 thrombocytopenia
  - Any laboratory evidence of hemolysis with more than a 3 gm/dL drop in hemoglobin requiring transfusion or steroids (or CTCAE hemoglobin level ≥ Grade 3).

- Grade 4: Any laboratory evidence of hemolysis requiring urgent medical intervention and one of the following:
  - Grade 3 creatinine level
  - Grade 4 platelets
  - Hemodynamic instability

3.5 DRUG ADMINISTRATION

3.5.1 NPC-1C (NEO-102)

3.5.1.1 NPC-1C (NEO-102) Drug Administration

All treatments will be administered on an outpatient basis except when admission is required for any reason. NPC-1C (NEO-102) will be administered approximately 30 minutes after the Gemcitabine infusion is completed (which will follow the nab-paclitaxel).

In Arm A only: Twenty (20) to 30 minutes prior to the start of each NPC-1C (NEO-102) infusion, all patients will receive the following pre-medications:

- Dexamethasone 10 mg IV
- Benadryl 50 mg IV (but can be reduced to 25 mg in case of sensitivity)
- Ranitidine 50 mg IV or equivalent

After completing pre-medications, NPC-1C (NEO-102) will be administered by intravenous continuous infusion in 250 mL of 0.9% sodium chloride USP using either a 0.20 or 0.22 non (or low) protein binding micron filter with a portable pump. The attachment of the infusion pump administration set to the i.v. bag and transport of the study drug to the patient will be performed as per standard study site procedures. Infusions of NPC-1C (NEO-102) will initially be administered at 0.5 mg/min. If the patient develops an infusion reaction related to NPC-1C (NEO-102), then the guidelines in Appendix D: Hypersensitivity Infusion Reaction Algorithm will be followed. Infusion rates may be increased as tolerated in 0.5 mg/min increments every 30 minutes to a maximum rate of 4 mg/min. Subsequent doses may be administered at the highest tolerated rate of infusion, and/or adjusted based on patient tolerance.

3.5.1.2 Vital Sign Monitoring (including blood pressure, pulse, respiratory rate)

- Pre infusion of study drug.
- Every 15 minutes (± 5 minutes) from start of infusion, times two (2). If vital signs are stable and no evidence of an adverse reaction is noted, vital signs can resume hourly until completion of infusion.
- If infusion of study drug is interrupted at any time, vital signs should continue to be taken every 15 minutes (± 5 minutes) during the interruption period and until one hour after the time infusion of study drug is re-started. Vital signs will continue to be assessed every 15 minutes until stable, at which time vital signs will be taken hourly until 1 hour after the completion of infusion. During hospitalization, vital signs will be taken and documented every 6-8 hours, or as clinically indicated.

3.5.1.3 NPC-1C (NEO-102) Infusion Reactions

- If the patient experiences a grade 2 or 3 adverse reaction during infusion, the infusion will be stopped and the patient will be treated accordingly as in Appendix E. Antipyretic, antihistamine and other therapies can be administered as indicated. If appropriate, the infusion may be restarted at half of the previous rate when the patient is able to continue. The infusion rate for the subsequent doses may be initiated at the highest tolerated rate.
- Patients who experience a grade 4 hypersensitivity reaction will be taken off the treatment with NPC-1C (NEO-102). The patient will be removed from the protocol and will be continued on Gemcitabine/Nab-paclitaxel as a standard of care therapy.
- Infusion reactions will be recorded as AEs in the case report form. Interventions should be documented as concomitant medications or concomitant treatments as appropriate.

3.5.2 Nab-paclitaxel (Abraxane)

Patients do not require premedication prior to Nab-paclitaxel administration, as hypersensitivity reactions are not expected, though initial antiemetic prophylaxis is recommended due to administration of gemcitabine following Nab-paclitaxel treatment.

If a severe hypersensitivity reaction occurs, the infusion should be stopped and not restarted as hypersensitivity reactions to Nab-paclitaxel can sometimes be fatal. For grade 1 or 2 hypersensitivity reactions, subsequent cycles may be administered using the premedication regimen typically used in the institution for Taxol.

Nab-paclitaxel will be administered according to the product labeling information, by intravenous infusion at a dose of 125mg/m^2 over approximately 30 minutes not to exceed 40 minutes.

3.5.3 Gemcitabine (Gemzar)

3.5.3.1 Gemcitabine Administration

Gemcitabine will generally be administered on an outpatient basis except when admission is required for any reason. Thirty minutes to one hour prior to the start of each Gemcitabine infusion, all patients will receive antiemetic primary prophylaxis: (preferred agents) Ondansetron 8 mg IV or 16–24 mg PO *or* Granisetron 2 mg PO or 1 mg IV for 1 dose.

After completing pre-medication, Gemcitabine will be administered according to its product labeling information, by intravenous infusion at a dose of 1000 mg/m^2 over approximately 30 minutes.

3.5.3.2 Special Precautions

Flu-type symptoms are reported for about 20% of patients. This includes fever, headache, back pain, chills, myalgia, and asthenia. Malaise and sweating are also commonly reported. Flu like symptoms will be treated symptomatically with acetaminophen and hydration as appropriate.

3.6 DOSING DELAYS AND DOSE MODIFICATIONS

3.6.1 Gemcitabine and Nab-paclitaxel Dose Modification

3.6.1.1 Gemcitabine and Nab-paclitaxel dosage adjustments for hematological toxicities

Gemcitabine and Nab-paclitaxel dosage adjustments for hematological toxicities are based on the granulocyte and platelet counts. Gemcitabine and Nab-paclitaxel dosage should be modified according to institutional standards of care, the Abraxane package insert located at: (http://www.abraxane.com/downloads/Abraxane_PrescribingInformation.pdf) specifically,(**Table 4** Dose Recommendation and Modifications for Neutropenia and/or Thrombocytopenia at the Start of a Cycle or within a Cycle for Patients with Adenocarcinoma of the Pancreas and **Table 5** Dose Modifications for Other Adverse Drug Reactions in Patients with Adenocarcinoma of the Pancreas) (select pages from package insert are included in Appendix F) and the investigator discretion. Toxicities will be graded using the NCI CTCAE Version 4.0. Two levels of dose modifications are permitted (according to the criteria listed in Table 3: Dose Level Reductions for Patients with Adenocarcinoma of the Pancreas contained in the Abraxane package insert (See Appendix F).

Based on experience in administering the Gemcitabine and nab-paclitaxel to patients after first line therapy with FOLFIRINOX, the majority of patients require dose delays, skipped doses and dose modifications[35]. If dosing modifications, dose delays or doses are skipped during Cycle 1 due to toxicity attributed to Gemcitabine/nab-paclitaxel, subsequent cycles **MAY** be given at the investigator's discretion as:

Gemcitabine: (1000 mg/m^2 IV on days 1 and 15 of a 28-day cycle)
Nab-paclitaxel (125 mg/m^2 IV on days 1 and 15 of a 28-day cycle)
} With doses modified as needed, as described above

With (ARM A) or without (ARM B) **NPC-1C** (NEO-102) (1.5 mg/kg IV on days 1 and 15 of a 28-day cycle).

If a toxicity requiring dose modification occurs following the second dose reduction of either study drug, further treatment should be discontinued. Any further dose modification requires prior Sponsor approval.

Exceptions to the need for dose-modification due to treatment-related non-hematologic toxicities are the following:

- Grade 3/4 electrolyte toxicities that can be corrected to Grade 1 or less within 24 hours.
- Grade 3 hypertension that can be controlled with oral medications and does not require treatment delay for > 7 days.
- Grade 3 diarrhea, nausea and vomiting unless refractory to anti-emetic therapy and unable to be corrected to Grade 1 or less within 48 hours.
- Grade 3 rise in creatinine, not corrected to Grade 2 or less after 2 liters of intravenous fluids within 24 hours.
- Grade 3 elevation in AST/ALT unless also ≥ 2 times the baseline level. (This is because patients who have liver metastases with Grade 2 transaminase levels are

eligible for study entry).

- Grade 3/4 elevation on ALP (Alkaline phosphatase).
- Grade 3/4 hypoalbuminemia.
- Grade 3 rash unless it does not return to ≤ Grade 2 after 1 week of symptomatic treatment.

If doses of gemcitabine/nab-paclitaxel are held/skipped for chemotherapy-related toxicity in patients assigned to Arm A, patients may receive the scheduled dose of NPC-1C (NEO-102) regardless of skipping the dose of gemcitabine/nab-paclitaxel. If a patient in Arm A discontinues gemcitabine/nab-paclitaxel due to gemcitabine/nab-paclitaxel toxicity, patients may continue to receive NEO-102 alone, at the PI discretion, according to protocol schedule until the patient meets off treatment criteria (see Section 3.9).

3.6.1.2 Peripheral Neuropathy

Nab-paclitaxel treatment should be withheld in patients who experience grade 3 peripheral neuropathy until neuropathy resolves to grade ≤2. Gemcitabine and NPC-1C administration can continue during this period. Nab-paclitaxel treatment may be resumed at the next lower dose level in subsequent cycles after the peripheral neuropathy improves to grade ≤2. For recurrence of severe (grade 3) one additional dose reduction may be made at the next lower dose level in subsequent cycles. If grade 3 peripheral neuropathy recurs after a second dose reduction treatment with nab-Paclitaxel must be discontinued, but patients may remain on protocol therapy with Gemcitabine with or without NPC-1C.

3.6.1.3 Supportive treatment for hematological toxicities: If the dosage of Gemcitabine/nab-paclitaxel is held due to grade 4 neutropenia, filgrastim may be given at a dose of 5- 10 mcg/kg (SC) daily during that cycle and after every Gemcitabine administration in the following cycles, at the discretion of the PI. The first dose of filgrastim should not be administered less than 24 hours following Gemcitabine/nab-paclitaxel, and filgrastim should not be administered within 24 hours before giving Gemcitabine/nab-paclitaxel. Calculated filgrastim doses may be rounded by ±10% to use the most economical combination of available products (commercially available products contain 300 mcg or 480 mcg). Blood transfusion and platelets transfusion will be allowed for grade 3-4 anemia and thrombocytopenia.

3.6.1.4 Supportive treatment for non-hematological toxicities: supportive treatment with IV fluid, anti-emetics, anti-diarrhea and acetaminophen will be administered as indicated.

In the case of flu like symptoms due to Gemcitabine infusion, patients may be treated with acetaminophen. If the treatment with Gemcitabine/nab-paclitaxel is held for > 21 days due to chemotherapy related toxicity, patients in Arm A may continue to receive NPC-1C (NEO-102) on schedule during subsequent cycles.

3.6.2 NPC-1C (NEO-102) Dose Modification (Arm A Only):

3.6.2.1 NPC-1C (NEO-102) expected adverse events

The most commonly reported clinical toxicities due to the use of NPC-1C (NEO-102are discussed in Section 1.2.4.

3.6.2.2 NPC-1C (NEO-102) dosage adjustments for hematological and non-hematological toxicities

- For all grade 3 non-hematologic toxicities and hematologic toxicities that is determined to be related to NPC-1C (NEO-102), NPC-1C (NEO-102) will be held until toxicities resolve to ≤ grade 1 for non-hematologic toxicities and hematological toxicities.
- Treatment for each specific toxicity will be administered per standard recommended therapy, as appropriate. Infusion reactions will be managed according to Appendix D.
- After the resolution of toxicities to ≤ grade 1 for non-hematologic toxicities and hematological toxicities, NPC-1C (NEO-102) will be administered in the following cycles as follows:
    - If NPC-1C (NEO-102) is being administered at 1.5 mg/kg, the dose will be reduced to 1 mg/kg in the following cycles.
    - If NPC-1C (NEO-102) is being administered at 1 mg/kg, no further dose reduction in NPC-1C (NEO-102) will be allowed. NPC-1C (NEO-102) will be discontinued and the patient can continue to receive Gemcitabine/nab-paclitaxel. Accordingly, the patient will be followed on study as indicated in section 3.8.
- If the treatment with NPC-1C (NEO-102) is delayed for > 14 days due to adverse events attributed (at least probably) related to NPC-1C (NEO-102) then NPC-1C (NEO-102) will be discontinued and the patient can continue to receive Gemcitabine and nab-paclitaxel. Accordingly, the patient will be followed on study as indicated in section 3.8.

3.6.3 General Guidelines for Combination Therapy modifications:

- Investigator discretion is permitted to determine which drug is the source for a given toxicity and to adjust the dosage of Gemcitabine, nab-paclitaxel with or without NPC-1C (NEO-102) accordingly.
- Treatment for each specific toxicity will be administered per standard recommended therapy, as appropriate.

3.7 ON-STUDY EVALUATIONS (SEE STUDY CALENDAR)

3.7.1 Baseline Evaluation

- Tumor marker profile: CA19-9.
- The baseline correlative studies as described in section 5.1.

3.7.1.1 History and physical exam with vital signs (obtained within 7 days prior to dosing).

3.7.1.2 Imaging studies (obtained within 28 days prior to dosing):

- CT scan of chest, abdomen and pelvis
- MRI if unable to obtain CT scan

3.7.2 Pre-Dosing Evaluation

3.7.2.1 Baseline Laboratory Assessment

Prior to initiation of Day1 Cycle 1 dosing, laboratory evaluation will be performed (if screening labs were performed > 72 hours) to include (Results are not required prior to administration of first dose (Cycle 1 Day 1 only) of study drug):

- CBC
- Urinalysis
- Electrolytes, BUN, creatinine

Baseline laboratory values obtained on Day 1 Cycle 1 will not affect the patient's eligibility to participate in the study after the patient has undergone Sponsor approval and been randomized and enrolled on the study. Baseline values will be used to determine dosing procedures for Gemcitabine/Abraxane according to Appendix F. Patients enrolled on Arm A will not receive the first dose of NEO-102 until initiation of Gemcitabine/Abraxane therapy.

3.7.3 Treatment Evaluations

3.7.3.1 History and physical exam with vital signs and weight on day 1 of each cycle.

Additional vital signs will be collected as per Section 3.5.1.2.

A symptom directed physical exam should be performed prior to any dose at the discretion of the investigator.

3.7.3.2 Laboratory evaluation on day 1 [post Cycle 1] (prior to dosing), and day 8* and 15 of every cycle (+/- 24 hours) (*will be performed if patient remains on Day 1, 8, and 15 dosing schedule of chemotherapy):

- Hematological profile: CBC with differential and platelet count, PT, aPTT, fibrinogen.
- Biochemical profile: electrolytes, BUN, creatinine, AST, ALT, ALP, total bilirubin, calcium, phosphorus, albumin, magnesium, uric acid, albumin, and LDH.

3.7.3.3 Hemoglobin levels within 24-48 hours in Arm A only after the 1st and 2nd dose of NPC-1C (NEO-102) (Cycle 1, day 2 or 3 and Cycle 1, day 16 or 17) [may be performed by local laboratory]

3.7.3.4 Tumor marker profile: CA19-9 every 2 cycles.

3.7.3.5 Correlative studies pre cycle 1 and 2 and at the end of the study as described in Section 5.2.

3.7.3.6 Imaging studies every 2 cycles

- CT scan of chest, abdomen and pelvis or MRI if unable to obtain CT scan.

3.7.3.7 Electrocardiogram (obtained at the visit the subject is taken off-treatment)

3.8 STUDY CALENDAR

	Pre-Study	Cycle 1[a] (±2 days)				Cycle 2 (±2 days)				Cycle 3 (and additional cycles) (±2 days)			Off Treatment Visit	At least 30 (±5) days after the last dose of study agent[l]
Day		**1**	**8**	**15**	**22**	**1**	**8**	**15**	**22**	**1**	**8**	**15**		
Gemcitabine		X	X	X	REST	X	X[m]	X	REST	X	X[m]	X		
nab-paclitaxel		X	X	X		X	X[m]	X		X	X[m]	X		
NPC-1C(NEO-102) (arm A only)		X		X		X		X		X		X		
Premedications[b]		X	X	X		X	X[m]	X		X	X[m]	X		
Informed consent IHC Screening Protocol Consent	X X													
Demographics	X													
Medical history	X													
Adverse event evaluation		X	X	X		X	X[m]	X		X	X[m]	X	X	X
Concomitant Medications	X	X	X	X		X	X[m]	X		X	X[m]	X	X	X
Physical exam	X	X	X[j]	X[j]		X	X[jm]	X[j]		X	X[jm]	X[j]	X	
Vital signs	X	X		X		X		X		X		X	X	
Height	X													
Weight	X	X				X				X			X	
Performance Status	X	X				X				X			X	
CBC w/differential[c], Platelets	X	X[a]	X	X		X	X[m]	X		X	X[m]	X	X	
PT, PTT, Fibrinogen	X		X[k]	X		X	X[k]	X		X	X[k]	X	X	
Serum chemistry[d]	X	X[a]	X	X		X	X[m]	X		X	X[m]	X	X	
Urinalysis		X												
Serum CA19-19	X									X				
Pregnancy Test (urine or serum)	X													
ECG	X												X[i]	
Restaging radiologic Evaluation[e]	X									X			X[k]	
IHC staining of tumor tissue for NPC-1C	X[h]													
HACA[f]		X											X	
Immunomonitoring[g]		X				X								

a: Baseline labs (CBC, electrolytes, BUN, creatinine, and urinalysis) will be repeated within 24 hours prior to the first dosing (if screening labs > 72 hours) (results are not required prior to drug administration). See section 3.7.1.
b: Premedications: dexamethasone 10 mg IV , diphenhydramine 50 mg IV and ranitidine 50mg or equivalent IV 20-30 minutes prior to NPC-1C(NEO-102). Antiemetic primary prophylaxis: (preferred agents) Ondansetron 8 mg IV or 16–24 mg po or Granisetron 2 mg PO or 1 mg IV for 1 dose. For details please refer to section 3.5.3.1.
c: Arm A only: Hgb will be drawn within 24-48 hrs after 1st and 2nd dose of NPC-1C (NEO-102)
d: Electrolytes, BUN, creatinine, AST, ALT, ALP, total bilirubin, calcium, phosphorus, albumin, magnesium, uric acid, albumin, and LDH.
e: CT scan chest, abdomen, pelvis; or MRI if unable to obtain a CT scan. See section 3.7.1.
f: Arm A only: HACA will be collected at baseline (prior to the first infusion) and at off treatment visit. See section 5.2.2 for details.
g: Arm A only : PBMCs and serum will be analyzed for immunomonitoring from patients prior to first treatment on C1D1 and prior to dose on C2D1. It is also optional to perform these analyses 8 weeks after the initiation of the study and in the end of the study treatment for patients at NIH only. See section 5.2.3 for details.
h: To be performed prior to other screening evaluations after signing IHC Screening Consent. Only if ≥ 20% will other screening evaluations be performed.
i: If subject is taken off study treatment at this evaluation, obtain an ECG for comparison with baseline.
j: A symptom directed physical exam should be performed prior to any dose at the discretion of the investigator: As indicated with hemolysis evaluation.
k: Only if clinically indicated.
l. Refer to Section 3.9 for Follow up Evaluations
[m] If dosing modifications, dose delays or doses are skipped during Cycle 1 due to toxicity attributed to gemcitabine/nab-paclitaxel, the investigator may decide it is in the patient's best interest to administer gemcitabine and nab-paclitaxel on a Day 1 and Day 15 (biweekly) schedule. In which case assessments will not be necessary on Day 8. The rationale and plan should be documented in the medical record and eCRF.

3.9 CRITERIA FOR REMOVAL FROM PROTOCOL THERAPY AND OFF STUDY CRITERIA

3.9.1 Criteria for removal from protocol therapy

- Unacceptable adverse event(s) as defined in the dose limiting toxicity section in the Phase I part (section 3.3.1) or the following criteria for the Phase IIB part:
    - Grade 4 infusion reaction due to NPC-1C (NEO-102).
    - Grade 4 non-hematologic toxicities due to NPC-1C (NEO-102) or the combination therapy.
    - Grade 3 non-hematologic toxicities due to NPC-1C (NEO-102) or the combination therapy that does not resolve to ≤ grade 1 within 14 days after holding the treatment.
    - Grade 4 hematologic toxicities due to NPC-1C (NEO-102) or the combination therapy that does not resolve to ≤ grade 2 after appropriate treatment with filgrastim or blood transfusion within 14 days after holding the treatment.
- Disease progression as determined by clinical evaluation or RECIST criteria (v1.1).
- Investigator decision: extraordinary medical circumstances: If at any time the constraints of this protocol are detrimental to the patient's health, the patient may be removed from the protocol therapy.
- Patient decides to withdraw from treatment.
- Intercurrent illness that prevents further administration of study treatment.

3.9.2 Off-Study Criteria

- Voluntary withdrawal of consent to participate in the study or the follow up period.
- Subject lost to follow up.
- Death.

Authorized staff must notify the Sponsor when a subject is taken off-study (please see CRF Manual).

3.10 FOLLOW UP EVALUATIONS

3.10.1.1 Patients who discontinue treatment with NPC-1C (NEO-102) and Gemcitabine/nab-paclitaxel due to toxicity will undergo disease evaluation every 1-3 months until the development of progressive disease, at which time they will continue to be followed for survival.

- All study subjects will be followed for overall survival only once active treatment has been completed (as indicated above).
- Patients will be followed until resolution of toxicity to at least Grade 1. This may be done by phone if appropriate. Patients must be evaluated for toxicity at least 30 days after the last dose of study agent for toxicity.
- Follow-up will be quarterly assessment of survival status. Every attempt will be made to contact patient/subject including: contacting referring physician, contacting emergency contact patient identified on admission, checking SSDI (Social Security Death Index) or Ancestry.com.
- Blood drawn for correlative studies during follow up visits as indicated in Section 5.2.

4 CONCOMITANT MEDICATIONS/MEASURES

4.1 PERMITTED CONCOMITANT MEDICATIONS

Permitted medications will include analgesics (opioid and non-opioid), antiemetics, antidiarrheals, pancreatic enzymes, probiotics, multivitamins, adjuvant analgesics, if for the purpose of co-analgesia. Permitted supplements are omega 3 fatty acids and HMB (ß-hydroxy ß-methylbutyrate) Juven®, and any nutrient-dense medical food supplement, such as ProSure® or Ensure® or BOOST®, if taken for at least one month before entering the study.

Concomitant medications for other medical conditions are permitted as clinically indicated, subject to specific protocol requirements outlined in this study.

4.2 CONCOMITANT MEDICATIONS NOT PERMITTED

The following medications are not permitted: Human growth hormone, anabolic steroids, cyproheptadine (Periactin®) and supplements other than those mentioned above are not to be used during any phase of the study. So called “off label” or adjuvant medications for malaise,

fatigue, anorexia/cachexia are not to be added. No alternative or complementary medicine products with purported appetite stimulating effects are permitted. In addition the following are also excluded:

- Any investigational agent other than NPC-1C (NEO-102).
- Any elective major surgical procedure deemed not lifesaving.
- Supplements not specifically permitted (above).

Should the investigator feel that it is in the patient's best interests to receive one of the above-mentioned therapies, the patient must be withdrawn from the study, unless permission to remain has been granted in writing by the Sponsor and IRB.

5 BIOSPECIMEN COLLECTION

5.1 IMMUNOHISTOCHEMISTRY WITH NPC-1C:

IHC with NPC-1C may be performed by the study site or at UT Southwestern Medical Center. If sending slides to UTSW: four (4) unstained slides (5-6 micron thickness) or tissue block will be sent to UT Southwestern Medical Center, Dr. Jose Torrealba and Gloria Daniels for IHC staining with NPC-1C and interpretation after subject has signed the NPC-1C screening consent using the request form in Appendix C, to:

Dr. Jose Torrealba and Gloria Daniels

Clements University Hospital
6201 Harry Hines Blvd. 4th Floor Room 04.246
Dallas, TX 75390-9234
Phone: 214-633-6342

email: Jose.Torrealba@UTSouthwestern.edu; Gloria.Daniel@UTSouthwestern.edu

The samples must be accompanied by a completed request form (sample form in Appendix C). Results can be expected within 5 business days of receipt of the tissue and completed IHC Request form at UT Southwestern Medical Center.

5.1.1 Summary of Assay:

This assay employs a direct immunohistochemical technique using a Biotin Labeled detection system (Roche Diagnostics Cat. #11418165001). The method is summarized in Figure 3:

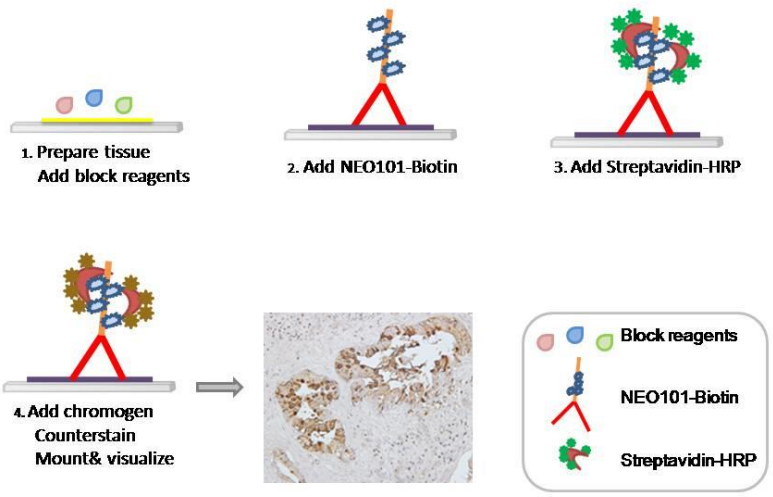


Figure 3: Immunohistochemistry with NPC-1C

5.1.2 Procedure for slide submission

Site personnel will complete the header on the NPC-1C Immunohistochemical Staining Request form (See Appendix C), and complete the information for the return of the results of the IHC testing.

Slides or unstained tissue block will be sent with the completed form in bubble envelopes supplied by the Sponsor to the address above.

5.2 CORRELATIVE STUDIES FOR RESEARCH

5.2.1 Blood Collection and Processing:

A maximum of 116 mL of blood are mandatory samples for collection from each subject in Arm A as described in Appendix E. These samples are processed, shipped according to instructions in the Laboratory Manual, and frozen for later analysis. Date and exact time of each blood draw should be recorded on the blood tubes. After processing as outlined in the Laboratory Manual samples will be shipped to NCI for immunomonitoring or will be stored as described in detail in the Laboratory Manual. A summary is as follows:

- Arm A Only: Serum aliquots for HACA are to be stored at -70°C or colder until shipped to sponsor, as instructed in the Laboratory Manual. Cryovials containing serum aliquots from each time-point should be placed into a pre-labeled gridded cardboard storage box supplied by the sponsor.
- Arm A Only: Serum aliquots for cytokines are to be centrifuged and shipped as described in the Laboratory Manual until ready to be tested.

5.2.2 Immunogenicity Testing (HACA) for Arm A only (to be performed at Precision Biologics, Inc):

- Peripheral blood will be collected from all subjects **in Arm A only** in a red top tube to assess immunogenicity (Human Anti-chimeric Antibodies/HACA) as described in Appendix E. Immunogenicity studies (HACA) will be collected at baseline (prior to the first infusion) and at off treatment visit. A commercially available qualified ELISA assay will be used at BioReliance Corp to measure HACA responses against NPC-1C(NEO-102) in the serum of subjects.
- At the time of shipping, transfer equal numbers of cryovial aliquots from each time-point to each of the pre-labeled gridded cardboard storage box supplied by the sponsor.
- Samples will be shipped in subject batches after all samples for the subject have been collected and processed. Sponsor will make contact with the site and initiate the shipping process.
- The blood processing and inventory logs should be partially completed after samples were processed to serum. At the time of shipping, the remaining sections of the logs should be completed. These forms are displayed in the Laboratory Manual provided to each site.
- All shipments should be on dry ice and via FedEx overnight, using the sponsor's FedEx account number according to instructions in the Laboratory Manual.
- Do not ship on Fridays or the day before holidays.

5.2.3 Immunomonitoring of samples (Arm A only; to be performed at NCI):

Non-immune based therapies have been shown to have significant effects on tumor-specific immune responses. There is increasing evidence demonstrating that under certain circumstances chemotherapy might have potential beneficiary effects on tumor specific immune responses.

Both PBMCs and serum will be analyzed for immunomonitoring from patients in Arm A prior to first treatment and 4 weeks after initiation (C2D1). It is also optional to perform this analysis 8 weeks after the initiation of the study and at the end of treatment for patients at NIH, at the PI discretion.

Frequency, phenotype and function of different immune cells (including CD8+ T cells, CD4+ T cells, Tregs and MDSCs) will be analyzed in Dr. Greten's laboratory at NCI, phone 301-451-4723. In addition, approximately 10 ml of each patient blood sample will be transported from CCR, NCI by courier to the Clinical Services Program, SAIC-Frederick on the NCI-Frederick campus for

future analysis for the ELISPOT assays. These assays will be conducted at the Kopp's lab: SAIC-Frederick, Phone: 301-846-1707. Please follow the instructions in Table 5 for the specific amount of blood samples and tubes.

5.2.3.1 Immune response to mesothelin by ELISPOT:

Mesothelin is a tumor differentiation antigen that is highly expressed in pancreatic cancer. Mesothelin expression by immunohistochemistry is present in approximately 100% of ductal pancreatic adenocarcinomas, which makes it an attractive target to test for immune response. Accordingly, this study will investigate the effect of the treatment of NPC-1C(NEO-102), nab-paclitaxel and Gemcitabine on the patient's immune response to Mesothelin tested by ELISPOT at baseline, post cycle 1, post cycle 2 (optional).

5.2.3.2 CD4, CD8 and regulatory (CD4+ CD25high) T-cell:

Regulatory T cells have been shown to inhibit the activation and function of T cells that participate in antigen-specific immune responses. Higher levels of Tregs have been reported in the PBMCs of patients with several types of tumors. The number and phenotype of T-cells in PBMCs from patients in this study will be determined by flow cytometry analysis. Approximately 100,000 cells will be re-suspended in staining buffer (phosphate-buffered saline containing 3% fetal bovine serum) and stained for CD4, CD8, CD25, and FoxP3. The ratios between Tregs and CD4 Effector cells and the ratios between Tregs and CD8 Effector cells will also be analyzed.

5.2.3.3 Myeloid-derived suppressor cells (MDSCs):

MDSCs have been shown to inhibit T cell responses in tumor-bearing mice, but little is known about these cells in humans. Human MDSCs have been described in patients with many tumors including pancreatic cancer. This study will investigate the effect of the treatment of NPC-1C(NEO-102), nab-paclitaxel and Gemcitabine on the Myeloid derived suppressor cells in patients with pancreatic cancer. 7-Flow cytometry will performed by LSRII FACS or similar technology with FlowJo (or similar software) analysis.

5.2.2.4 Cytokines: Cytokines will be measured in each patient serum including: INFα, INFγ, IL-4, and GM-CSF.

5.2.4 Summary of correlative studies

The laboratories performing the testing, sample time points, blood volumes and tube requirements are specified in Appendix E.

Directions for handling and shipping of research blood samples from patients in Arm A enrolled at participating sites for analysis at NCI is described in detail in the Laboratory Manual.

5.3 SAMPLE STORAGE, TRACKING AND DISPOSITION

All specimens obtained in the protocol are used as defined in this protocol. Any specimens that are remaining at the completion of the protocol will be destroyed or moved to a tissue study as described below. The study will remain open so long as sample or data analysis continues. Samples from consenting subjects will be stored until they are no longer of scientific value or if a subject withdraws consent for their continued use. If a patient withdraws consent the

participant's data will be excluded from future distributions, but data/samples that have already been distributed for approved research use will not be able to be retrieved. The PI will report any loss or destruction of samples to the institutional IRB as soon as he/she is made aware of such loss. Samples will also be reported as lost if they are lost in transit between facilities or misplaced by a researcher. Freezer problems, lost samples or other problems associated with samples will also be reported according to the institutions' policies and procedures.

Samples collected during the course of this study will not be sent with personal identifiers, but will include the patient's study number, date and time of sample acquisition. Blood processing, sample labeling, and collection for immunologic studies will be conducted as outlined in the study Section 5.2. Samples will be tracked and considered the responsibility of the principal investigator. Tissue samples sent to UT Southwestern Medical Center for IHC screening of NPC-1C antibody/antigen target with unique study identification number as assigned by the study team as per Appendix C for medical record tracking at the testing site.

All cryopreserved samples are tracked for freezer location and storage criteria. All samples are stored in monitored freezers/refrigerators either in the freezers at Precision Biologics, Inc. or designee, or the investigator's laboratory, at specified temperatures with alarm systems in place. All samples (blood or tissue) are documented in a secure computer database with identification and storage location, with computer backup according to established standards. Samples submitted to Precision Biologics, Inc. are tracked on hard copy case report forms in locked files with access to designated sponsor personnel.

At the termination of this protocol, if additional studies are to be performed on any samples retaining subject identifiers, obtained during the conduct of this trial, a Request to Conduct Research for Stored Human Samples Specimens, or Data Collected in a Terminated NCI-IRB Protocol will be submitted. Any new uses of samples collected during the course of this trial must be reviewed and approved by the participating site's IRB.

6 DATA COLLECTION AND EVALUATION

6.1 DATA COLLECTION

Data will be collected, entered onto either paper Case Report Forms or via electronic data capture (EDC) [Axiom's Go Cubed Clinical Trial Suite] provided by the sponsor, and monitored according to Section 7.4. All data will be kept secure. Personal identifiers will not be used when collecting and storing data. An enrollment log will be maintained in the regulatory binder/file which is the only location of personal identifiers with unique subject identification number.

The investigators at each site will be responsible for the collection, maintenance and quality control of the study data. Data will be prospectively collected and recorded on r CRFs by each sites' personnel responsible for study data. Toxicity and treatment data will be entered onto study CRFs within at least 2 weeks of each patient encounter.

6.2 RESPONSE CRITERIA

For the purposes of this study, patients should be re-evaluated for response every 8 weeks of the treatment (two cycles of therapy, 6 doses of Gemcitabine/nab-paclitaxel and 4 doses of NPC-1C (NEO-102)). In addition to a baseline scan, confirmatory scans should also be obtained at least 4 weeks following initial documentation of objective response.

Response and progression will be evaluated in this study using the new international criteria proposed by the revised Response Evaluation Criteria in Solid Tumors (RECIST) guideline (version 1.1) [*Eur J Ca* 45:228-247, 2009]. Changes in the largest diameter (unidimensional measurement) of the tumor lesions and the shortest diameter in the case of malignant lymph nodes are used in the RECIST criteria.

6.2.1 Definitions

Evaluable for toxicity: All patients will be evaluable for toxicity from the time of their first treatment with Gemcitabine/nab-paclitaxel with or without NPC-1C (NEO-102).

Evaluable for objective response: Only those patients who have measurable disease present at baseline, have received at least one cycle of therapy, and have had their disease re-evaluated will be considered evaluable for response. These patients will have their response classified according to the definitions stated below. (Note: Patients who exhibit objective disease progression prior to the end of cycle 1 will also be considered evaluable.)

6.2.2 Disease Parameters

Measurable disease: Measurable lesions are defined as those that can be accurately measured in at least one dimension (longest diameter to be recorded) as ≥20 mm by chest x-ray, as ≥10 mm with CT scan, or ≥10 mm with calipers by clinical exam. All tumor measurements must be recorded in millimeters (or decimal fractions of centimeters).

Malignant lymph nodes. To be considered pathologically enlarged and measurable, a lymph node must be ≥15 mm in short axis when assessed by CT scan (CT scan slice thickness recommended to be no greater than 2 mm). At baseline and in follow-up, only the short axis will be measured and followed.

Non-measurable disease. All other lesions (or sites of disease), including small lesions (longest diameter <10 mm or pathological lymph nodes with ≥10 to <15 mm short axis), are considered non-measurable disease. Bone lesions, leptomeningeal disease, ascites, pleural/pericardial effusions, lymphangitis cutis/pulmonitis, inflammatory breast disease, and abdominal masses (not followed by CT or MRI), are considered as non-measurable.

Note: Cystic lesions that meet the criteria for radiographically defined simple cysts should not be considered as malignant lesions (neither measurable nor non-measurable) since they are, by definition, simple cysts.

'Cystic lesions' thought to represent cystic metastases can be considered as measurable lesions, if they meet the definition of measurability described above. However, if non-cystic lesions are present in the same patient, these are preferred for selection as target lesions.

Target lesions. All measurable lesions up to a maximum of 2 lesions per organ and 5 lesions in total, representative of all involved organs, should be identified as **target lesions** and recorded and measured at baseline. Target lesions should be selected on the basis of their size (lesions with the longest diameter), be representative of all involved organs, but in addition should be those that lend themselves to reproducible repeated measurements. It may be the case that, on occasion, the largest lesion does not lend itself to reproducible measurement in which circumstance the next largest lesion which can be measured reproducibly should be selected. A sum of the diameters (longest for non-nodal lesions, short axis for nodal lesions) for all target lesions will be calculated and reported as the baseline sum diameters. If lymph nodes are to be included in the sum, then only the short axis is added into the sum. The baseline sum diameters will be used as reference to further characterize any objective tumor regression in the measurable dimension of the disease.

Non-target lesions. All other lesions (or sites of disease) including any measurable lesions over and above the 5 target lesions should be identified as **non-target lesions** and should also be recorded at baseline. Measurements of these lesions are not required, but the presence, absence, or in rare cases unequivocal progression of each should be noted throughout follow-up.

6.2.3 Methods for Evaluation of Measurable Disease

All measurements should be taken and recorded in metric notation using a ruler or calipers. All baseline evaluations should be performed as closely as possible to the beginning of treatment and never more than 4 weeks before the beginning of the treatment.

The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during follow-up.

CT - is the best currently available and reproducible methods to measure target lesions selected for response assessment. For this study helical Multi-detector CT will be performed with cuts of 5 mm in slice thickness for chest, abdomen and pelvis lesions and 2-3 mm thickness for head and neck lesions.

6.2.4 Response Criteria

6.2.4.1 Evaluation of Target Lesions

Complete Response (CR): Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to <10 mm.

Partial Response (PR): At least a 30% decrease in the sum of the diameters of target lesions, taking as reference the baseline sum diameters.

Progressive Disease (PD): At least a 20% increase in the sum of the diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. (Note: the appearance of one or more new lesions is also considered progressions).

Stable Disease (SD): Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum diameters while on study.

6.2.4.2 Evaluation of Non-Target Lesions

Complete Response (CR): Disappearance of all non-target lesions and normalization of tumor marker level. All lymph nodes must be non-pathological in size (<10 mm short axis).

Note: If tumor markers are initially above the upper normal limit, they must normalize for a patient to be considered in complete clinical response.

Non-CR/Non-PD: Persistence of one or more non-target lesion(s) and/or maintenance of tumor marker level above the normal limits.

Progressive Disease (PD): Appearance of one or more new lesions and/or *unequivocal progression* of existing non-target lesions. *Unequivocal progression* should not normally trump target lesion status. It must be representative of overall disease status change, not a single lesion increase.

Although a clear progression of "non-target" lesions only is exceptional, the opinion of the treating physician should prevail in such circumstances, and the progression status should be confirmed at a later time by the review panel (or Principal Investigator).

6.2.4.3 Evaluation of Best Overall Response

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

For Patients with Measurable Disease (i.e., Target Disease)

Target Lesions	Non-Target Lesions	New Lesions	Overall Response	Best Overall Response when Confirmation is Required*
CR	CR	No	CR	≥4 wks. Confirmation**
CR	Non-CR/Non-PD	No	PR	≥4 wks. Confirmation**
CR	Not evaluated	No	PR	
PR	Non-CR/Non-PD/not evaluated	No	PR	
SD	Non-CR/Non-PD/not evaluated	No	SD	Documented at least once ≥4 wks. from baseline**
PD	Any	Yes or No	PD	no prior SD, PR or CR

Any	PD***	Yes or No	PD
Any	Any	Yes	PD

* See RECIST 1.1 manuscript for further details on what is evidence of a new lesion.

** Only for non-randomized trials with response as primary endpoint.

*** In exceptional circumstances, unequivocal progression in non-target lesions may be accepted as disease progression.

Note: Patients with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be reported as "*symptomatic deterioration."* Every effort should be made to document the objective progression even after discontinuation of treatment.

For Patients with Non-Measurable Disease (i.e., Non-Target Disease)

Non-Target Lesions	New Lesions	Overall Response
CR	No	CR
Non-CR/non-PD	No	Non-CR/non-PD*
Not all evaluated	No	not evaluated
Unequivocal PD	Yes or No	PD
Any	Yes	PD
* 'Non-CR/non-PD' is preferred over 'stable disease' for non-target disease since SD is increasingly used as an endpoint for assessment of efficacy in some trials so to assign this category when no lesions can be measured is not advised		

6.2.5 Duration of Response

Duration of overall response: The duration of overall response is measured from the time measurement criteria are met for CR or PR (whichever is first recorded) until the first date that recurrent or progressive disease is objectively documented (taking as reference for progressive disease the smallest measurements recorded since the treatment started).

The duration of overall CR is measured from the time measurement criteria are first met for CR until the first date that progressive disease is objectively documented.

Duration of stable disease: Stable disease is measured from the start of the treatment until the criteria for progression are met, taking as reference the smallest measurements recorded since the treatment started, including the baseline measurements.

6.2.6 Progression-Free Survival (PFS)

PFS is defined as the duration of time from start of treatment to time of progression or death, whichever occurs first.

6.2.7 Overall Survival (OS)

Overall survival is defined as the duration of time from start of treatment to time of death.

6.3 TOXICITY CRITERIA

The following adverse event management guidelines are intended to ensure the safety of each patient while on the study. The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 will be utilized for AE reporting. All appropriate treatment areas should have access to a copy of the CTCAE version 4.0. A copy of the CTCAE version 4.0 can be downloaded from the CTEP web site (http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm#ctc_40).

6.3.1 Suspected adverse reaction

Suspected adverse reaction means any adverse event for which there is a reasonable possibility that the drug caused the adverse event. For the purposes of IND safety reporting, 'reasonable possibility' means there is evidence to suggest a causal relationship between the drug and the adverse event. A suspected adverse reaction implies a lesser degree of certainty about causality than adverse reaction, which means any adverse event caused by a drug.

7 SAFETY REPORTING REQUIREMENTS/DATA AND SAFETY MONITORING PLAN

7.1 DEFINITIONS

7.1.1 Adverse Event

An adverse event is defined as any reaction, side effect, or untoward event that occurs during the course of the clinical trial associated with the use of a drug in humans, whether or not the event is considered related to the treatment or clinically significant. For this study, AEs will include events reported by the patient, as well as clinically significant abnormal findings on physical examination or laboratory evaluation. A new illness, symptom, sign or clinically significant laboratory abnormality or worsening of a pre-existing condition or abnormality is considered an AE. All AEs must be recorded on the AE case report form.

All AEs, including clinically significant abnormal findings on laboratory evaluations, regardless of severity, will be followed until satisfactory resolution. AEs starting from the first dose of drug (Gemcitabine, abraxane, NEO-102) up to 30 days following the last dose of study drug should be recorded in the Axiom electronic database.

An abnormal laboratory value will be considered an AE if the laboratory abnormality is characterized by any of the following:

- Results in discontinuation from the study
- Is associated with clinical signs or symptoms
- Requires treatment or any other therapeutic intervention
- Is associated with death or another serious adverse event, including hospitalization.
- Is judged by the Investigator to be of significant clinical impact
- If any abnormal laboratory result is considered clinically significant, the investigator will provide details about the action taken with respect to the test drug and about the patient's outcome.

7.1.2 Unexpected adverse reaction

An adverse event or suspected adverse reaction is considered "unexpected" if it is not listed in the investigator brochure or is not listed at the specificity or severity that has been observed; or, if an investigator brochure is not required or available, is not consistent with the risk information described in the general investigational plan or elsewhere in the current application. "Unexpected", also refers to adverse events or suspected adverse reactions that are mentioned in the investigator brochure as occurring with a class of drugs or as anticipated from the pharmacological properties of the drug, but are not specifically mentioned as occurring with the particular drug under investigation.

7.1.3 Serious

An Unanticipated Problem or Protocol Deviation is serious if it meets the definition of a Serious Adverse Event or if it compromises the safety, welfare or rights of subjects or others.

7.1.4 Serious Adverse Event

An adverse event or suspected adverse reaction is considered serious if in the view of the investigator or the sponsor, it results in any of the following:

- Death,
- A life-threatening adverse drug experience
- Inpatient hospitalization or prolongation of existing hospitalization
- Persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
- A congenital anomaly/birth defect.
- Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered a serious adverse drug experience when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

7.1.5 Disability

A substantial disruption of a person's ability to conduct normal life functions.

7.1.6 Life-threatening adverse drug experience

Any adverse event or suspected adverse reaction that places the patient or subject, in the view of the investigator or sponsor, at immediate risk of death from the reaction as it occurred, i.e., it does not include a reaction that had it occurred in a more severe form, might have caused death.

7.1.7 Protocol Deviation (NIH Definition)

Any change, divergence, or departure from the IRB approved research protocol. To accommodate changes for patient schedules, holidays and unforeseen weather incidences, any change or divergence in the scheduling or conduct of the examinations, tests, scans or treatment described in this protocol will not be considered a protocol deviation if performed +/- 2 days of the scheduled time point..

7.1.8 Non-compliance (NIH Definition)

The failure to comply with applicable NIH Human Research Protections Program (HRPP) policies, IRB requirements, or regulatory requirements for the protection of human research subjects.

7.1.9 Unanticipated Problem

Any incident, experience, or outcome that:

- Is unexpected in terms of nature, severity, or frequency in relation to

  (a) the research risks that are described in the IRB-approved research protocol and informed consent document; Investigator's Brochure or other study documents, and

  (b) the characteristics of the subject population being studied; **AND**
- Is related or possibly related to participation in the research; **AND**
- Places subjects or others at a g*reater risk of harm* (including physical, psychological, economic, or social harm) than was previously known or recognized.

7.2 REPORTING CRITERIA TO THE SPONSOR

7.2.1 Reporting to the Sponsor

An investigator must **immediately** report to the sponsor (Precision Biologics, Inc.) any unanticipated problem, serious adverse event, dose limiting toxicity, related unexpected events, or any instance of hemolysis, whether or not considered drug related occurring from the time of on-study to 30 days after the last dose of study treatment, including those listed in the protocol or investigator brochure and must include an assessment of whether there is a reasonable possibility that the study drug caused the event. A report will be submitted via electronic data capture (EDC) [Axiom's Go Cubed Clinical Trial Suite] with supporting documentation e-mailed or faxed to the sponsor within one week (7 calendar days) of the Investigator becoming aware of the event. An

investigator must also report to the sponsor any deviation or changes from the protocol regimen without prior agreement by the sponsor and prior review and documented approval by the institution's IRB, except where necessary to eliminate an immediate hazard to trial subjects, or when the change(s) involve only logistical or administrative aspects of the trial (e.g. change of telephone numbers).

Deviations, Unanticipated problems, SAEs, DLTs, related unexpected events, instances of hemolysis should be reported via electronic data capture (EDC) [Axiom's Go Cubed Clinical Trial Suite] with supporting documentation sent to:

Phil Arlen, MD, Medical Sponsor
e-mail: parlen@Precision-Biologics.com
Tel: (301) 728-4883
FAX: (240-669-9828)
Cc: kcui@Precision-Biologics.com;azaki@Precision-Biologics.com; smavroukakis@Precision-Biologics.com

Study endpoints that are serious adverse events (e.g. all-cause mortality) must be reported in accordance with the protocol unless there is evidence suggesting a causal relationship between the drug and the event (e.g. death from anaphylaxis). In that case, the investigator must immediately report the death to the sponsor.

The sponsor shall promptly investigate all safety information received and report follow up information in an IND safety report as soon

as relevant information is available. If the results of the sponsor's investigation show that an adverse event not initially determined to be reportable is later identified as reportable, the sponsor shall report such experience in a written safety report as soon as possible, but in no event later than 15 calendar days after the determination is made.

Planned hospital admissions or surgical procedures for an illness or disease which existed before the subject was enrolled in the trial or before study drug was given, are NOT to be considered AEs unless they occur at a time other than the planned date.

7.2.1.1 Adverse Event Recording

Adverse events, both serious and non-serious, and deaths will be captured from the first dose of study drug up to and including 30 days after the last dose of study drug. All serious adverse events will be monitored until they are resolved or are clearly determined to be due to patient's stable or chronic condition or intercurrent illness(es). Any adverse event that occurs at any time after completion of 30 days after the last dose of study drug, that the investigator considered to be related to study medication, should be reported to the sponsor.

For all serious and non-serious adverse events, the investigator must determine both the intensity of the event and the relationship of the event to study drug administration.

Intensity for each adverse event will be determined by using the National Cancer Institute Common Terminology Criteria for Adverse Events v4.0 (CTCAE) as a guideline, wherever

possible. In those cases where the CTCAE criteria do not apply, intensity should be defined according to the following criteria:

Mild	Grade 1, asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
Moderate	Grade minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL.
Severe	Grade 3 Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self care ADL.
Life-threatening	Grade 4, Life-threatening consequences; urgent intervention indicated.
Death	Grade 5 Death related to AE.

Relationship to study drug administration will be determined and recorded as follows:

Unrelated	The AE is clearly NOT related to the study drug, no temporal relationship exists, and can be attributed to alternative cause(s).
Unlikely	The current state of knowledge about the drug and the patient's disease indicates that a relationship is unlikely.
Possibly	A reaction that follows a plausible temporal sequence from administration of the study drug and follows a known response pattern to the suspected study drug. The reaction might have been produced by the patient's clinical state or other modes of therapy administered to the patient.
Probably	A reaction that follows a plausible temporal sequence from administration of the study drug and follows a known response pattern to the suspected study drug. The reaction cannot be reasonably explained by the known characteristics of the patient's clinical state or other modes of therapy administered to the patient.
Definitely	An adverse event that is clearly related to the study drug with temporal relationship to the administration of the study drug, follows a known pattern of response and no alternative causes.

7.3 IND SAFETY REPORTS

The sponsor shall be responsible for notifying all participating investigators and the FDA in a written IND safety report of:

1) Any adverse experience associated with the use of the drug that is both serious and unexpected; or
2) Any finding from tests in laboratory animals that suggests a significant risk for human subjects, including reports of mutagenicity, teratogenicity, or carcinogenicity.

Each notification will be made as soon possible and in no event later than 15 calendar days after the sponsor's initial receipt of the information.

In each written IND safety report, all safety reports previously filed with the IND concerning a similar adverse experience will be noted, and the significance of the adverse experience will be analyzed in light of the previous, similar reports.

- *Telephone and facsimile transmission safety reports.* The sponsor shall also notify FDA by telephone or by facsimile transmission of any unexpected fatal or life-threatening experience associated with the use of the drug as soon as possible but in no event later than 7 calendar days after the sponsor's initial receipt of the information.
- *Reporting format or frequency.* FDA may request a sponsor to submit IND safety reports in a format or at a frequency different than that required under this paragraph. The sponsor may also propose and adopt a different reporting format or frequency if the change is agreed to in advance by the director of the new drug review division in the Center for Drug Evaluation and Research responsible for review of the IND.

7.4 DATA AND SAFETY MONITORING PLAN

7.4.1 Principal Investigator/Research Team

The clinical research team will meet on a regular basis when patients are being actively treated on the trial to discuss each patient. Decisions about dose level enrollment and dose escalation if applicable will be made by the sponsor based on the toxicity data from prior patients at all participating sites. Individual investigators shall not proceed to treat a new subject until they have received sponsor approval and dose assignment as outlined in Appendix B.

All data will be collected in a timely manner and reviewed by the principal investigator or a lead associate investigator. Adverse events will be reported as required by the investigator's institutional policies and procedures. Any safety concerns, new information that might affect either the ethical and or scientific conduct of the trial, or protocol deviations and violations will be immediately reported to the investigator's IRB and to the Sponsor.

The principal investigator will review adverse event and response data on each patient to ensure safety and data accuracy. The principal investigator will personally conduct or supervise the investigation and provide appropriate delegation of responsibilities to other members of the research staff.

7.4.2 Administrative Sponsor Requirements

7.4.2.1 Sponsor Study monitoring

The Sponsor will review all serious adverse events and will monitor the data and toxicities to identify trends at least weekly during treatment of subjects. The participating sites' PI(s) and the coordinating sponsor will discuss all toxicities experienced after the first 6 subjects have been treated in in Arm A to collaboratively determine proceeding with enrollment. In the event of a DLT, the participating site PIs will be notified within 24 hours of the nature of the event. The coordinating sponsor will be responsible for revising the protocol as needed to maintain safety.

Monitoring and auditing procedures implemented by Precision Biologics, Inc. or its designee will be followed in order to comply with GCP guidelines. On-site checking of case report forms for completeness and clarity and consistency as compared with source documents, and clarification of administrative matters will be performed.

The study will be monitored by Precision Biologics, Inc. or its designee on a regular basis throughout the study period. Monitoring will be done by personal visits from a representative of the sponsor (site monitor) who will review the source documents. Source documentation includes but is not limited to the subject's clinic and/or office chart, hospital chart, informed consent forms, treatment notes, laboratory reports, pharmacy records, radiographs, and any other records maintained to conduct and evaluate the clinical study. The investigator must ensure the accuracy and completeness of the data reported, and its consistency with the source documentation. The primary source document for this study will be the subject's medical records. If separate research records are maintained by the investigator(s) both the medical record and the research records will be monitored/audited for the purposes of the study. The site monitor will ensure that the investigation is conducted according to protocol design and regulatory requirements by frequent communications (letter, telephone, and fax).

All unused study drug and other study materials are to be returned to Precision Biologics, Inc. after the clinical phase of the study has been completed.

7.4.2.2 On-site audits

Regulatory authorities, the IEC/IRB, and/or Precision Biologics's clinical quality assurance group may request access to all source documents, printouts of any data entry forms, and other study documentation for on-site audit or inspection. Direct access to these documents must be guaranteed by the Investigator, who must provide support at all times for these activities.

7.4.2.3 Data entry completion

For subjects who provide informed consent and were not entered/randomized into the study, the reason the subject was not entered/randomized, i.e., did not meet one or more inclusion criteria, met one or more exclusion criteria, or other (e.g., lost to follow up, consent withdrawn), will also be collected and maintained on the Screening/Study Log.

It is the Investigator's responsibility to ensure the accuracy, completeness, and timeliness of the data reported for each subject. Source documentation supporting the data should indicate the subject's participation in the study and should document the dates and details of study procedures, adverse events, and patient status.

The Investigator, or designated representative, should complete the data entry as soon as possible after information is collected, preferably within 2 weeks of study visit. Any outstanding entries must be completed immediately after the final examination. An explanation should be given for all missing data.

The Investigator's Study File will contain documents as outlined in ICH ECP E6 Section 8, including the protocol/amendments, Data Query Forms, Institutional Review Board and governmental approval with correspondence, sample informed consent, sponsor correspondence

records, staff curriculum vitae and authorization forms and other appropriate documents/correspondence, etc.

7.5 DRUG ACCOUNTABILITY

Accountability for the study drug at the study center is the responsibility of the Investigator. The Investigator will ensure that the study drug is used only in accordance with this protocol. Where allowed by site SOPs, the Investigator may choose to assign some of the drug accountability responsibilities to a pharmacist or other appropriate individual. Drug accountability records indicating the drug's delivery date to the center, inventory at the center, use by each subject, and return to Precision Biologics (or disposal of the drug, if approved by Precision Biologics) will be maintained by the participating site. These records will adequately document that the subjects were provided the doses as specified in the protocol and should reconcile all study drug received from Precision Biologics. Accountability records will include dates, quantities, batch/serial numbers, expiration dates (if applicable), and patient numbers. The sponsor or its designee will review drug accountability at the site on an ongoing basis during monitoring visits.

All unused study drug will be retained at the site until inventoried by the monitor. All unused or expired study drug will be returned to Precision Biologics or if authorized, disposed of at the study site as hazardous waste in accordance with governing regulations.

7.5.1.1 Premature closure of the study

This study may be prematurely terminated, if in the opinion of Precision Biologics, there is sufficient reasonable cause. The Investigator may terminate his/her participation for reasonable cause. The terminating party must provide written notification documenting the reason for study termination.

Circumstances that may warrant termination include, but are not limited to:

- Determination of unexpected, significant, or unacceptable risk to subjects;
- Failure to enter subjects at an acceptable rate;
- Insufficient adherence to protocol requirements;
- Insufficient and/or inadequate evaluable data; or
- Plans to modify, suspend or discontinue the development of the study drug.

8 STATISTICAL SECTION

The primary objective of this phase 2.5 study is to determine if the combination of NPC-1C and gemcitabine plus nab-paclitaxel is potentially able to improve the overall survival for patients who have pancreatic cancer over gemcitabine plus abraxane alone. The trial will be conducted as a 2-arm randomized multi-institution trial of NPC-1C plus gemcitabine and nab-paclitaxel vs. gemcitabine and nab-paclitaxel. Since a phase 2.5 trial is meant to identify a trend in a randomized, controlled fashion, any suggestion of positive findings will be evaluated for the potential to conduct a larger, subsequent multi-institutional definitive trial through an established cooperative group mechanism.

Based upon results in the literature, patients who would be eligible to be randomized on this trial would be expected to have an estimated 4.5 to 4.8 month median survival with gemcitabine alone, but this may be enhanced somewhat with the addition of nab-paclitaxel. The goal of this study will be to determine if the use of NPC-1C along with gemcitabine and nab-paclitaxel will result in patients having an increased median survival of 8 months vs. an estimated 5 months without NPC-1C. Kaplan-Meier curves and a two-tailed log-rank test will be the primary analysis methods. Assuming exponential survival curves, the hazard rate for gemcitabine plus nab-paclitaxel would be estimated to be 0.1386, or approximately a 14% probability of dying each month when the median survival time is 5 months. If we assume that the arm with NPC-1C will be associated with a median survival of 8 months, this corresponds to a hazard rate of 0.0866 and the resulting hazard ratio for the comparison of the two overall actuarial curves would be 1.60. Following the principals of a phase 2.5 design, to compare these curves and detect a difference with a 0.10 one-tailed log-rank test, a total of 45 evaluable subjects per arm (90 total) will need to be randomized over a thirty month period and a maximum follow-up of 42 months (12 months after the last patient has enrolled), with occurrence of 82 total deaths on both arms, in order to have 80% power to compare the curves.

The trial will be monitored by the NCI/CCR DSMB for toxicity on an annual basis, and will also perform one planned interim analysis for futility and for efficacy at a midpoint in the trial. The initial evaluation for safety of the combination will take place after treatment of the first 6 patients in Arm A. If ≥2 of the first 6 patients on Arm A experience either of the toxicities listed in Section 3.3.1.1, the study will be paused pending modification discussions with the IRB and FDA.

The first overall evaluation for toxicity will take place at the first annual DSMB meeting after 10 patients have been enrolled and treated on each arm. The goal will be to confirm that the toxicity among the two arms is not significantly different. If the NPC-1C arm exhibits a significantly greater fraction of patients experiencing a grade 3 or higher toxicity than the other arm, whether based on a specific toxicity or any toxicity, then the trial will be closed to further accrual until an amendment can be made to lessen the toxic effects of NPC-1C.

A single evaluation for futility will also be undertaken to permit the trial to stop accrual in the event that there is very low probability of detecting an advantage to using NPC-1C. At the first annual DSMB meeting taking place after 23 evaluable patients have been enrolled on each arm and potentially followed for at least 6 months, if the hazard ratio for survival comparing the two arms exceeds 1.00, and is favoring the arm without NPC-1C, then the trial will no longer enroll any other patients as it would be unlikely to be able to demonstrate a gain in survival compared to the arm without NPC-1C.

A single evaluation for efficacy will also be performed at the first annual DSMB meeting held after approximately 23 patients have been enrolled on each arm and followed for 6 months. Should the p-value for the comparison of the two arms be <0.005, then the DSMB should recommend that the trial will be closed for the presence of early, strong efficacy benefit for the arm with NPC-1C.

It is expected that all 90 patients can be accrued onto this trial in thirty months. In order to allow for a very small number of inevaluable patients, the accrual ceiling will be set at 94 patients.

9 MULTI-INSTITUTAL GUIDELINES

9.1 COLLABORATIVE AGREEMENT

The investigational study agent (NPC-1C (NEO-102)) is provided by Precision Biologics, Inc. to participating sites under a negotiated research agreement.

Participating sites agree to conduct the Clinical Trial in accordance with applicable provisions of ICH E6 (R1): FDA Good Clinical Practice and they agree to comply with all applicable U.S., state and local laws, regulations and guidelines.

The sponsor (or designee) will be responsible monitoring and quality assurance of all data at participating sites in accordance with the clinical monitoring plan. Monitoring will be done in compliance with current FDA Good Clinical Practice Guidelines (E6 (R1) and the sponsor will communicate any clinically significant findings from clinical monitors to the participating sites in a timely manner.

The sponsor will provide the participating sites with current copy of the Investigator's Brochure for the investigational agent and any later revisions and addenda to the IB during the course of the study.

The sponsor will assume responsibility for any alteration in or amendment to the protocol, which will undergo review by the participating sites. Prior to such alteration or amendment becoming effective they must be approved in writing by the relevant participating sites IRB(s) and submitted to the FDA.

The sponsor will be responsible for the data, and scientific reporting of all results/data obtained from the Clinical Trial will be a collaborative effort with the investigators of the participating sites. All publications based on the results of the clinical trial must be reviewed and approved by the sponsor prior to submission for publication.

9.2 IRB APPROVALS, AMENDMENTS AND CONSENTS:

Participating institutions will provide the Sponsor with copies of the initial local IRB approvals and semi-annual or annual continuing review approvals. Registration will be halted at any participating institution in which a current continuing approval is not on file with the Sponsor. Only one version of the protocol will be the correct version; amendments must be initiated upon receipt from the Sponsor. Each site will be responsible for its own IRB submissions.

9.3 PATIENT REGISTRATION:

All participating institutions must register patients with the sponsor as specified under section 2.3. Such patients will be treated, monitored, and managed according to the guidelines of this protocol, after signing a current version of the informed consent.

9.4 DRUG DISTRIBUTION:

Site PI's or their designees will order the study drug (NPC-1C(NEO-102)) from Precision Biologics, Inc. by completing and sending by fax or e-mail the Clinical Drug Request. The drug will be shipped to the pharmacy for each institution. Contact information: Precision Biologics, Inc., Phone: (301) 728-4883 (cell), FAX: 240-428-1552, e-mail: parlen@Precision-Biologics.com; azaki@ Precision-Biologics.com; kcui@Precision-Biologics.com; smavroukakis Precision-Biologics.com.

9.5 DATA COLLECTION AND TOXICITY REPORTING:

This protocol will be conducted as a single research effort and data from each participating site will be included in the analysis of results. All patients must meet eligibility requirements as demonstrated on the protocol's Eligibility Checklist (Appendix B) and all patients must sign an Informed Consent before entering the study. All toxicity and event data must be documented and transcribed on the Case Report Forms supplied by the Sponsor to the participating institutions, within two weeks of each patient's visit. In addition, complete records will be maintained on each patient at the participating institutions. These will consist of hospital records with any supplementary information obtained from outside laboratories, radiology reports or physicians' records. These records will serve as the primary source of material that forms the basis for the research record. All data collection forms and records will be audited on-site at participating institutions and should be made available at the time of the study audit. Reportable Serious Adverse Events (SAE) and reporting requirements are defined in Section 7. All reportable SAEs must be reported by the participating centers directly to the institution's IRB according to the relevant IRB requirements, and to the trial sponsor as specified in Section 7 IND Sponsor Reporting Criteria.

10 HUMAN SUBJECTS PROTECTIONS

10.1 RATIONALE FOR SUBJECT SELECTION

Subjects of both genders and from all racial and ethnic groups are eligible for this trial if they meet the eligibility criteria. No groups are being excluded from participation in the trial. Efforts will be made to extend the accrual to a representative population.

10.2 PARTICIPATION OF CHILDREN

Individuals under the age of 18 will not be eligible to participate in this study because they are unlikely to have pancreatic cancer, and because of unknown toxicities in pediatric patients.

10.3 EVALUATION OF BENEFITS AND RISKS/DISCOMFORTS

Patients will receive evaluation of their disease at the participating site. This protocol may or may not benefit an individual, but the results may help the investigators learn more about the disease and develop new treatments for patients with this disease. Benefit cannot be promised nor can the chance of benefit be accurately predicted. All care will be taken to minimize side effects, but they can be unpredictable in nature and severity. This study may involve risks to patients, which are

currently unforeseeable. Patients will be examined and evaluated prior to enrollment. All evaluations to monitor the treatment of patients will be recorded in the patient chart. If patients suffer any physical injury as a result of the participation in this study, immediate medical treatment is available at the participating sites. Although no compensation is available, any injury will be evaluated and treated in keeping with the benefits or care to which patients are entitled under applicable regulations.

In all publications and presentations resulting from this trial, patients' anonymity will be protected to the maximum extent possible. Authorized personnel from the National Cancer Institute (NCI), the Sponsor, and Food and Drug Administration (FDA) or other regulatory authorities may have access to research files in order to verify that patients' rights have been safeguarded.

10.4 CONSENT AND ASSENT PROCESS AND DOCUMENTATION

The investigational nature and research objectives of this trial, the procedures and treatments involved and their attendant risks, discomforts, benefits, and potential alternative therapies will be carefully explained to the patient.

10.4.1 IHC Screening Consent

Consent must be obtained prior to obtaining and analyzing tissue samples (2 or more unstained slides or tissue block). Telephone consent may be employed in order to screen outside samples, according to institutional/IRB procedures. In such cases, a protocol investigator will review the Screening Sample Consent form by telephone. The consent signatures will be witnessed and a copy will be faxed to the investigator's site and the original sent by mail to the PI. Prospective subjects who consent to sample testing will be documented on the IHC Screening Log Sheet.

10.4.2 Study Screening Informed Consent

A signed informed consent document will be obtained by a study investigator prior to entry onto the study. The PI or associate investigator will meet with the patient to discuss the protocol treatment and alternative options in detail. It will be stated clearly that participation in the research study is voluntary and that participants can withdraw from the study without losing benefits they would otherwise be entitled to. The patient and family members when applicable will be encouraged to ask questions, and additional meetings to discuss the treatment options will be arranged as necessary. The original signed consent will be maintained according to institutional policy.

Subjects who complete the standard consent and undergo study screening must be documented on the Study Screening Log sheet.

11 PHARMACEUTICAL AND INVESTIGATIONAL DEVICE INFORMATION

11.1 NPC-1C (NEO-102) ARM A ONLY

11.1.1 Source:

NPC-1C is an investigational agent that will be provided by Precision Biologics, Inc., manufactured and filled by Cytovance Biologics, Oklahoma City, OK. The study drug may only be requested by the Principal Investigator (or an associate investigator or study pharmacist) from the Study Centers' Pharmacy. The Study Center Pharmacy will document distribution of all study drug.
The Study Center Pharmacy can request drug supplies by e-mailing or phoning the request to Precision Biologics:

Anjum Zaki

E-mail: azaki@Precision-Biologics.com

Phone: 301-917-6779

Cc e-mails to kcui@Precision-Biologics.com and smavroukakis@Precision-Biologics.com.

After notification, Precision Biologics will complete and forward the shipment request form to Almac. Almac personnel will send confirmation of shipment including a FED-EX tracking number to designated study site personnel with a cc to the Sponsor when shipment is sent.

11.1.2 Toxicity:

The clinical experience with NPC-1C (NEO-102) when given as monotherapy is summarized in Section 1.2.4.

Five (5) patients received NPC-1C (NEO-102) with gemcitabine on this study prior to the addition of nab-paclitaxel to the regimen. The following suspected adverse events were observed:

Adverse event (grade)	Total # of events (N=5)	Relationship to Study Drug
Anxiety (grade 1)	1	Possibly
Constipation (grade 1)	1	Possibly
Edema (grade 1)	1	Possibly
Fatigue (grade 1)	1	Possibly
Hyperpigmentation of hand creases (grade 1)	1	Possibly
Mucositis (grade 1)	1	Possibly
Nausea (grade 1)	4	Possibly
Skin peeling (grade 1)	1	Possibly
Vomiting (grade 1)	1	Possibly

11.1.3 Formulation and preparation:

The biotherapeutic antibody is purified and formulated in sodium citrate, sodium chloride and Tween-80, pH 6.5. The concentration of the NPC-1C (NEO-102) final vialed product is 10 mg/mL, in 10 mL per vial, thus 100 mg/vial (single use vials). Each vial is labeled with the drug

name and concentration, sponsor name, and storage conditions. The vials are also labeled "for investigational use only".

11.1.4 Stability and Storage and Infusion:

Vials of NPC-1C(NEO-102) drug product should be shipped frozen in CREEDO coolers (-20 ºC) and stored frozen at -20 ºC ± 10 ºC (short excursions outside this range [but still < 0 ºC] can be tolerated but must be reported to sponsor) until ready for patient administration.

The investigator or pharmacist will be required to inventory all shipments with receipts. NPC-1C (NEO-102) must be stored in the freezer according to the manufacturer's instructions and kept in a secure area with access restricted to designated study personnel. The investigator or pharmacist will keep accurate records of vials and quantities of the study drug used by each study subject. The clinical monitor will ensure the use of the medication records is accurate and the investigator or pharmacist is accountable. DO NOT ADMINISTER IF THERE IS VISUAL PRECIPITATE IN THE BAG OR VIAL. Any unused agent should be discarded as medical waste and should not be reused or refrozen for later use. Although there is no current data to demonstrate interaction with polyvinyl chloride (PVC) infusion equipment or leaching of plasticizers such as di(2-ethylhexyl) phthalate (DEHP) from intravenous equipment, this study will use administration sets with a fluid pathway suitable for administering paclitaxel; polyolefin composition (e.g., polypropylene or polyethylene) or polyolefin-lined during antibody administration. NPC-1C (NEO-102) infusion should be initiated within 2 hours after thawing. The dose level and infusion start and stop times must be recorded in the source documents.

11.1.5 Incompatibilities:

There are no known incompatibilities with other agents.

11.1.6 Reconstitution

Prior to administration to study subjects, vial(s) should be thawed at room temperature, gently inverted 10 times, and the required volume for the NPC-1C (NEO-102) dose diluted in 250 mL 0.9% sodium chloride USP. NPC-1C (NEO-102) should be administered intravenously. NPC-1C (NEO-102) administration should be completed within 8 hours of thaw. DO NOT ADMINISTER IF THERE IS VISUAL PRECIPITATE IN THE BAG OR VIAL. Any unused agent should be discarded as medical waste and should not be reused or re-frozen for later use.

11.1.7 Administration:

NPC-1C (NEO-102) will be administered by intravenous continuous infusion using either a 0.20 or 0.22 low protein binding micron filter with a portable pump. The attachment of the infusion pump administration set to the i.v. bag and transport of the study drug to the patient will be performed as per standard study site procedures. Infusions of NPC-1C(NEO-102) should be administered initially at 0.5 mg/min. Infusion rates may be adjusted as tolerated in 0.5 mg/min increments every 30 minutes to a maximum rate of 4 mg/min. Subsequent doses may be administered at the highest tolerated rate of infusion, and/or adjusted based on patient tolerance. If the patient develops an infusion reaction related to NPC-1C(NEO-102), the infusion rate will be adjusted as described in section 3.5.1.3.

11.2 GEMCITABINE

Gemcitabine is a nucleoside analogue that exhibits antitumor activity which is cell phase-specific for the S-phase and for the G1/S-phase boundary of cell division. It is metabolized intracellularly by nucleoside kinases to the active diphosphate (dFdCDP) and triphosphate (dFdCTP) nucleosides. Cytotoxic effect of gemcitabine is due to a combination of 2 actions of the dFdCDP and dFdCTP nucleosides, which leads to inhibition of DNA synthesis. Please refer to the FDA-approved package insert for additional information.

11.2.1 Source:

Commercially Available

11.2.2 Toxicity:

- Hematologic: Myelosuppression is usually mild to moderate and is more pronounced for the granulocyte count. Thrombocytopenia is also commonly reported.
- Dermatologic: A rash is seen in about 25% of patients and is associated with pruritis in about 10% of patients. The rash is usually mild, not dose-limiting, and responds to local therapy. Desquamation, vesiculation, and ulceration have been reported rarely. Alopecia is reported in <1% of patients.
- Gastrointestinal: Nausea and vomiting are reported in about two-thirds of patients and requires therapy in about 20% of patients. It is rarely (<1%) dose-limiting, and is easily manageable with standard antiemetics. Diarrhea is reported in 8% of patients, constipation in 6%, and oral toxicity in 7%. Anorexia has also been seen.
- Renal: Elevation of serum creatinine or BUN; Mild proteinuria and hematuria; Hemolytic uremic syndrome.
- Hepatic: Abnormalities of hepatic transaminase enzymes occur in two-thirds of patients, but they are usually mild, nonprogressive, and rarely necessitate stopping treatment. However, gemcitabine should be used with caution in patients with impaired hepatic function.
- Pulmonary: Bronchospasm after injection has been reported in less than 1% of patients and is usually mild and transient, but parenteral therapy may be required. Dyspnea within a few hours of injection is reported in 10% of patients. It is usually mild, short- lived, rarely dose-limiting, usually abates without any specific therapy. Cough and rhinitis are also commonly reported.
- Neurologic: Somnolence has been reported in 10% of patients, and insomnia is common. Dizziness, agitation, paresthesia, confusion, convulsion, and coma have also been reported.
- Cardiovascular: A few cases of hypotension were reported. Some cases of myocardial infarction, congestive heart failure, and arrhythmia have been reported, but there is no clear evidence that

- Gemcitabine causes cardiac toxicity. Peripheral edema is reported in about 30% of patients. Some causes of facial edema have also been reported. Edema is usually mild to moderate, rarely dose limiting, sometimes painful, and reversible after stopping the gemcitabine treatment.
- Other: Flu-type symptoms are reported for about 20% of patients. This includes fever, headache, back pain, chills, myalgia, asthenia. Malaise and sweating are also commonly reported. Alopecia, fatigue and shortness of breath have also been reported.

11.2.3 Formulation and preparation:

Gemcitabine should be reconstituted by adding 0.9 % sodium chloride injection USP (without preservatives) to a maximum concentration of 40 mg/mL. Reconstituted solution should be stored at controlled room temperature and used within 24 hours; unused portion should be discarded. Do not refrigerate as crystallization may occur. Shake to dissolve; may further dilute down to 0.1 mg/mL using 0.9 % sodium chloride injection USP (without preservatives).

11.2.4 Stability and Storage:

Gemcitabine is supplied in a sterile form for intravenous use only. Vials of Gemcitabine contain either 200 mg or 1 g of gemcitabine HCl (expressed as free base) formulated with mannitol (200 mg or 1 g, respectively) and sodium acetate (12.5 mg or 62.5 mg, respectively) as a sterile lyophilized powder. Hydrochloric acid and/or sodium hydroxide may have been added for pH adjustment. When prepared as directed, gemcitabine solutions are stable for 24 hours at controlled room temperature 20° to 25°C (68° to 77°F). Discard unused portion. Solutions of reconstituted gemcitabine should not be refrigerated, as crystallization may occur.

11.2.5 Administration procedures:

Gemcitabine is administered intravenously over 30 minutes.

11.2.6 Incompatibilities:

May react with strong oxidizing agents (e.g., peroxides, permanganates, nitric acid, etc.).

11.3 PACLITAXEL PROTEIN-BOUND PARTICLES FOR INJECTABLE SUSPENSION (ALBUMIN-BOUND (NAB-PACLITAXEL, ABRAXANE®)

11.3.1 Source:

nab-Paclitaxel will be purchased by the institutions' pharmacy from commercial sources.

11.3.2 Toxicity:

Bone marrow suppression (primarily neutropenia) is dose-dependent and a dose-limiting toxicity of ABRAXANE. In clinical studies, Grade 3-4 neutropenia occurred in 34% of patients with

metastatic breast cancer (MBC), 47% of patients with non-small cell lung cancer (NSCLC), and 38% of patients with pancreatic cancer.

Nervous System

Sensory neuropathy is dose- and schedule-dependent. The occurrence of Grade 1 or 2 sensory neuropathy does not generally require dose modification.

Sepsis

Sepsis occurred in 5% of patients with or without neutropenia who received ABRAXANE in combination with gemcitabine. Biliary obstruction or presence of biliary stent were risk factors for severe or fatal sepsis.

Pneumonitis

Pneumonitis, including some cases that were fatal, occurred in 4% of patients receiving ABRAXANE in combination with gemcitabine.

Hypersensitivity

Severe and sometimes fatal hypersensitivity reactions, including anaphylactic reactions, have been reported.

Hepatic Impairment

Because the exposure and toxicity of paclitaxel can be increased with hepatic impairment, administration of ABRAXANE in patients with hepatic impairment should be performed with caution.

Formulation:

Each mL of the reconstituted formulation will contain 5 mg paclitaxel per milliliter.

Calculate the exact total dosing volume of 5 mg/mL suspension required for the patient: Dosing volume (mL) = Total dose (mg)/5 (mg/mL).

The reconstituted suspension should be milky and homogenous without visible particulates. If particulates or settling are visible, the vial should be **gently** inverted again to ensure complete resuspension prior to use. Discard the reconstituted suspension if precipitates are observed. Discard any unused portion.

Inject the appropriate amount of reconstituted ABRAXANE into an empty, sterile intravenous bag [plasticized polyvinyl chloride (PVC) containers, PVC or non-PVC type intravenous bag]. The use of specialized DEHP-free solution containers or administration sets is not necessary to prepare or administer ABRAXANE infusions. The use of an in-line filter is not recommended.

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration whenever solution and container permit.

Stability

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

Stability of Reconstituted Suspension in the Vial

Reconstituted ABRAXANE in the vial should be used immediately, but may be refrigerated at 2ºC to 8ºC (35.6º–46.4ºF) for a maximum of 8 hours if necessary. If not used immediately, each vial of reconstituted suspension should be replaced in the original carton to protect it from bright light. Discard any unused portion.

Stability of Reconstituted Suspension in the Infusion Bag

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

Administration

ABRAXANE will be administered intravenously over 30 minutes.

If ABRAXANE administration does not commence within 30 minutes after product preparation, the product container should be gently inverted (several repetitions) to re-suspend the drug particles before commencing drug administration.

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13 APPENDICES

13.1 APPENDIX A-PERFORMANCE STATUS CRITERIA

ECOG Performance Status Scale		**Karnofsky Performance Scale**	
Grade	Descriptions	Percent	Description
0	Normal activity. Fully active, able to carry on all pre-disease performance without restriction.	100	Normal, no complaints, no evidence of disease.
		90	Able to carry on normal activity; minor signs or symptoms of disease.
1	Symptoms, but ambulatory. Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature (e.g., light housework, office work).	80	Normal activity with effort; some signs or symptoms of disease.
		70	Cares for self, unable to carry on normal activity or to do active work.
2	In bed <50% of the time. Ambulatory and capable of all self-care, but unable to carry out any work activities. Up and about more than 50% of waking hours.	60	Requires occasional assistance, but is able to care for most of his/her needs.
		50	Requires considerable assistance and frequent medical care.
3	In bed >50% of the time. Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.	40	Disabled, requires special care and assistance.
		30	Severely disabled, hospitalization indicated. Death not imminent.
4	100% bedridden. Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.	20	Very sick, hospitalization indicated. Death not imminent.
		10	Moribund, fatal processes progressing rapidly.
5	Dead.	0	Dead.

13.2 APPENDIX B: ELIGIBILITY CHECKLIST

PRECISION BIOLOGICS, INC.	Protocol No. PB1201	Site Number ☐☐	Principal Investigator

Protocol Title: *A Multicenter randomized phase II Study of NPC-1C in Combination with Gemcitabine and nab-Paclitaxel versus Gemcitabine and nab-Paclitaxel alone in Patients with Metastatic or Locally Advanced Pancreatic Cancer Previously Treated with FOLFIRINOX*

PATIENT ENROLLMENT FORM

Date of Screening Visit (MM/DD/YYYY): ☐☐/☐☐/☐☐☐☐

Patient Initials	Sex	Weight	Height
☐☐☐ F M L	☐ Male ☐ Female	☐☐☐.☐ ☐ lb ☐ kg	☐☐☐.☐ ☐ cm ☐ inches
Consent Version:		**Date Consent Signed:** (MM/DD/YYYY) ☐☐/☐☐/☐☐☐☐	
Consent Completed? ☐Yes ☐No			

Race	Ethnicity
☐ White ☐ Black or African American ☐ Asian	☐ Hispanic or Latino
☐ Native Hawaiian or Other Pacific Islander ☐ Unknown	☐ Not Hispanic or Latino
☐ American Indian or Alaska Native ☐ Other: _____	☐ Unknown

Completed Patient Registration Form and attached documents to be emailed (preferable) or faxed

Attention:	Email Addresses	Fax Number	Date Sent
Dr. Phil Arlen Precision Biologics, Inc.	parlen@precision-biologics.com	240-428-1522	

Total Pages (including cover): _____

Attachments:

☐ History and Physical notes ☐ ECG and report ☐ NPC-1C IHC result
☐ Screening Lab Reports ☐ Pathology report
☐ Scan reports

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Based on review of the eligibility information contained in this checklist, I confirm the patient status of study enrollment as indicated below:

☐ Patient may NOT be enrolled

☐ Patient may be enrolled: Subject Number assigned: ☐☐☐

Dose of NPC-1C to be administered to patient: ☐.☐ mg/kg

Randomization:

☐ **Arm A**- Gemcitabine, Nab-paclitaxel, NPC-1C/NEO-102

☐ **Arm B**- Gemcitabine, Nap-paclitaxel

Comments: _____

Sponsor Signature: _____ **Date:** _____

- Subject may proceed to treatment only after the Sponsor reviews and approves eligibility by:
  - Return of the completed and signed "For Sponsor Use Only" via e-mail or fax
- Please place a copy of the sponsor signed form, and if applicable the email authorization, in the subject's research record.

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PRECISION BIOLOGICS, INC.	**Protocol No.** PB1201	**Site Number** ☐☐	**Principal Investigator**

	INCLUSION CRITERIA	**Yes**	**No**	**N/A**
1	Does the subject have a history of recurrent, locally advanced unresectable or metastatic adenocarcinoma of the pancreas who has progressed after primary therapy with FOLFIRINOX or FOLFIRINOX-like regimen or were intolerant of it? Is current disease measurable?	☐ ☐	☐ ☐	
2	Tumor stains ≥ 20% positive for NPC-1C antibody/antigen target as determined by the Department of Pathology.	☐	☐	
3	Is ≥ 18 years of age?	☐	☐	
4	Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1 (Appendix A).	☐	☐	
5	Have an anticipated life expectancy of greater than 8 weeks.	☐	☐	
6	Patients must have recovered from any acute toxicity related to prior therapy. Toxicity should be ≤ grade 1 or ≤ grade 2 for peripheral neuropathy returned to baseline.	☐	☐	
7	If female, is post-menopausal, surgically sterilized or willing to use an effective method of contraception (i.e., a hormonal contraceptive, intra-uterine device, diaphragm with spermicide, or condom with spermicide, or abstinence) for the duration of the study and for 3 months after the end of treatment?	☐	☐	☐
8	If male, has agreed to use barrier method for contraception for the duration of the study and for 3 months after the end of treatment?	☐	☐	☐
9	Patient must be willing to sign a written informed consent	☐	☐	
10	Hemoglobin ≥ 8.5 g/dL (may be receiving supportive therapy)	☐	☐	
11	ANC ≥ 1,500 K/uL	☐	☐	
12	Platelets ≥ 100 K/uL	☐	☐	
13	Total bilirubin ≤ 2 mg/dL	☐	☐	
14	ALT/AST ≤ 3 times ULN or ≤ 5 times ULN in the setting of liver metastases	☐	☐	
15	Creatinine ≤ 1.5 mg/dL or creatinine clearance > 40 mL/min/1.73 m2 for patients with creatinine levels above institutional normal, as calculated by the Cockcroft Gault formula.	☐	☐	

PRECISION BIOLOGICS, INC.	**Protocol No.** PB1201	**Site Number** ☐☐	**Principal Investigator**

EXCLUSION CRITERIA		**Yes**	**No**	**N/A**
16E	Has patient received a second line chemotherapy after progressing on or not tolerating treatment with FOLFIRINOX as a first line? (Prior adjuvant/neoadjuvant gemcitabine or gemcitabine-based radiation will not be counted as first line therapy)	☐	☐	
17E	Has known brain metastases?	☐	☐	
18E	Has had major surgery within 4 weeks of enrollment?	☐	☐	
19E	Has greater than grade 2 clinically detectable ascites at time of enrollment?	☐	☐	
20E	Has received Gemcitabine for palliative treatment? Has received Gemcitabine for treatment or recurrent or metastatic disease? Is within 3 months of receiving Gemcitabine in the adjuvant or neo-adjuvant setting?	☐ ☐ ☐	☐ ☐ ☐	
21E	Has uncontrolled concomitant illness including, but not limited to, ongoing or active infection, symptomatic congestive heart failure, unstable angina pectoris, or cardiac arrhythmia?	☐	☐	
22E	Has a serious medical or psychiatric illness, that could, in the Investigator's opinion, potentially interferes with the completion of treatment according to this protocol?	☐	☐	
23E	Had invasive malignancies within the past 3 years (with the exception of non-melanoma skin cancers or non-invasive bladder cancer)?	☐	☐	
24E	Pregnant or breast-feeding?	☐	☐	☐
25E	Has had any chemotherapy, or systemic corticosteroids within 2 weeks of study entry?	☐	☐	
26E	Has acquired, hereditary, or congenital immunodeficiencies including cellular immunodeficiencies, hypogammaglobulinemia and dysgammaglobulinemia?	☐	☐	
27E	Has prior history of a documented hemolytic event?	☐	☐	
28E	Has history of hypersensitivity to human or mouse antibody products?	☐	☐	
29E	Is HIV-positive, both receiving anti-retroviral therapy or not?	☐	☐	

Signature below indicates that source documentation of the eligibility criteria in this checklist has been verified.

Name (printed)	Signature	Date

The inclusion/exclusion criteria have been reviewed. I agree with the above assessments and recommend this patient for enrollment.

Investigator Signature	Date

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13.3 APPENDIX C: NPC-1C IMMUNOHISTOCHEMICAL STAINING REQUEST

NPC-1C Immunohistochemical Staining Request

Tumors are considered positive for binding of NPC-1C if more than 20% of the tumor cells stain positively using the immunohistochemical assay.

Principal Investigator:	**Sponsor:** Precision Biologics, Inc	**Protocol No:** PB1201
Protocol Title: A Multicenter Randomized Phase II Study of NPC-1C in Combination with Gemcitabine and nab-Paclitaxel versus Gemcitabine and nab-Paclitaxel alone in Patients with Metastatic or Locally Advanced Pancreatic Cancer Previously Treated with FOLFIRINOX		
Patient Identification Number ☐		**Screening Site Number** ____ **Fund Code**: Dr. Muhammad Beg
Date Tumor Tissue Obtained: ☐☐ ☐☐ ☐☐☐☐ **Tumor Site Obtained for IHC:** ☐ **Site Submitting Request (include contact name and site):** _____ _____ _____ **Contact Phone Number:** _____		
Screening Consent Complete: ☐ Yes ☐ No	**Consent Date:**	

RESULTS: Immunohistochemical staining is performed on sections from outside block.

Approximately ___ % of the tumor cells exhibit _____ intense staining.

INTERPRETATION:

THE TEST / RESULT IS _____FOR BINDING OF NPC-1C.

Pathologist Signature/Date

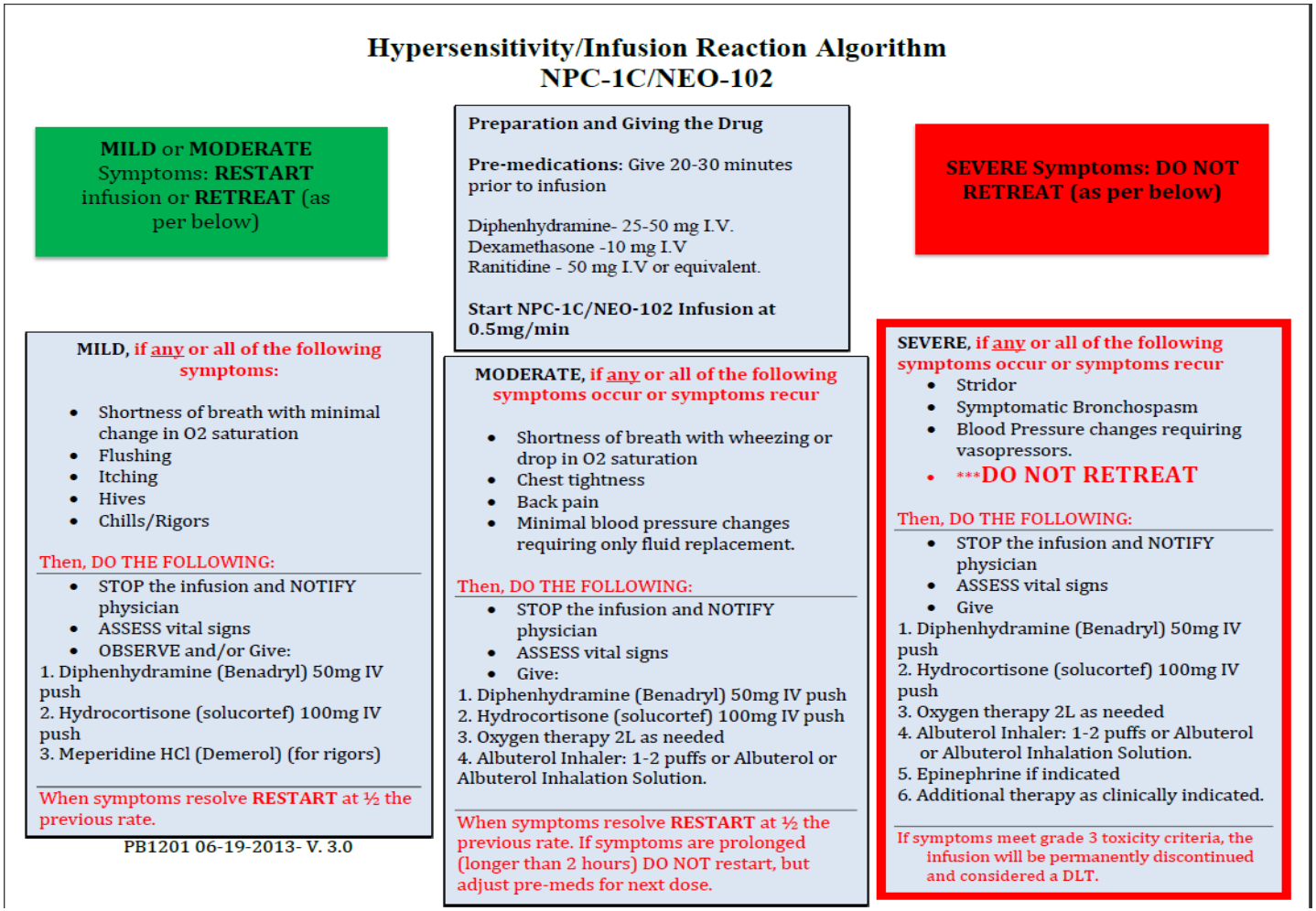
_____ / _____

RETURN RESULTS via Fax and/or E-mail to:
(to be completed by the Screening Site, prior to submission of slides/tissue block)

_____
_____
_____
_____

v. 7.0 11-3-14

13.4 APPENDIX D: HYPERSENSITIVITY/INFUSION REACTION ALGORITHM



13.5 APPENDIX E: SUMMARY OF CORRELATIVE STUDIES

Tissue Sample Type	Test	Lab performing testing	Tubes ALL SITES: *(except NCI)*	Tubes NCI Site ONLY:	Timing of Blood Draws	Storage and Shipping
Blood	Immune Response to Mesothelin by ELISPOT	NCI (Dr. Kopp Lab)	CPT/ Heparin tubes (green tops) **16 mL (2-8mL tubes)**	EDTA (purple tops) **20mL (2-10mL tubes)**	C1D1 C2D1 *(optional)* C3D1, Off Tx **	Process as per SOP #5 Ship as per SOP #6
	CD4, CD8 and regulatory T-Cells (CD4+ CD25high)	NCI (Dr. Greten Lab)	CPT/ Heparin tubes (green tops) **16 mL (2-8mL tubes)**	EDTA (purple tops) **20mL (2-10mL tubes)**	C1D1 C2D1 *(optional)* C3D1, Off Tx **	Process as per SOP #5 Ship as per SOP #6
	Myeloid-derived suppressor cells (MDSC) Quantification	NCI (Dr. Greten Lab)	CPT/ Heparin tubes (green tops) **16 mL (2-8mL tubes)**	EDTA (purple tops) **20mL (2-10mL tubes)**	C1D1 C2D1 *(optional)* C3D1, Off Tx **	Process as per SOP #5 Ship as per SOP #6
	Cytokines	NCI (Dr. Greten Lab)	SST (red top tubes) **10 mL (2- 5mL tubes)**	SST (red top tubes) **10 mL (2-5mL tubes)**	C1D1 C2D1 *(optional)* C3D1, Off Tx **	Process as per SOP #4; Ship as per SOP #6
Blood	HACA (Arm A Only)	Precision Biologics, Inc.	SST (red top tube)-5 mL (1-**5mL tube)**	SST (red top tube)-5 mL (1-**5mL tube)**	C1D1 Off Tx	Process as per SOP #2; Store and Ship Frozen (-70ºC) as per SOP #3

** It is also optional to perform these analyses at C3D1 and at the end of treatment in patients participating at the NIH, at the PI discretion.

13.6 APPENDIX F: EXCERPTED FROM ABRAXANE FOR INJECTABLE SUSPENSION (PACKAGE INSERT)

(http://www.abraxane.com/downloads/Abraxane_PrescribingInformation.pdf

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use ABRAXANE safely and effectively. See full prescribing information for ABRAXANE.

ABRAXANE® for Injectable Suspension (paclitaxel protein-bound particles for injectable suspension) (albumin-bound)
Initial U.S. Approval: 2005

WARNING: NEUTROPENIA
See full prescribing information for complete boxed warning.

- **Do not administer ABRAXANE therapy to patients with baseline neutrophil counts of less than 1,500 cells/mm^3. (4)**
- **It is recommended that frequent peripheral blood cell counts be performed to monitor the occurrence of bone marrow suppression. (4, 5.1, 6.1, 6.2, 6.3)**

DO NOT SUBSTITUTE FOR OR WITH OTHER PACLITAXEL FORMULATIONS.

---------- RECENT MAJOR CHANGES ----------

• Dosage and Administration (2.4, 2.8)	12/2014
• Warnings and Precautions, Hepatic Impairment (5.6)	12/2014

---------- INDICATIONS AND USAGE ----------

ABRAXANE is a microtubule inhibitor indicated for the treatment of:

- Metastatic breast cancer, after failure of combination chemotherapy for metastatic disease or relapse within 6 months of adjuvant chemotherapy. Prior therapy should have included an anthracycline unless clinically contraindicated. (1.1)
- Locally advanced or metastatic non-small cell lung cancer (NSCLC), as first-line treatment in combination with carboplatin, in patients who are not candidates for curative surgery or radiation therapy. (1.2)
- Metastatic adenocarcinoma of the pancreas as first-line treatment, in combination with gemcitabine. (1.3)

---------- DOSAGE AND ADMINISTRATION ----------

- Metastatic Breast Cancer: Recommended dosage of ABRAXANE is 260 mg/m^2 intravenously over 30 minutes every 3 weeks. (2.1)
- Non-Small Cell Lung Cancer: Recommended dosage of ABRAXANE is 100 mg/m^2 intravenously over 30 minutes on Days 1, 8, and 15 of each 21-day cycle; administer carboplatin on Day 1 of each 21-day cycle immediately after ABRAXANE. (2.2)
- Adenocarcinoma of the Pancreas: Recommended dosage of ABRAXANE is 125 mg/m^2 intravenously over 30-40 minutes on Days 1, 8 and 15 of each 28-day cycle; administer gemcitabine on Days 1, 8 and 15 of each 28-day cycle immediately after ABRAXANE. (2.3)
- Do not administer ABRAXANE to any patient with AST > 10 x ULN or bilirubin > 5 x ULN. Do not administer ABRAXANE to patients with metastatic adenocarcinoma of the pancreas who have moderate to severe hepatic impairment. For diseases other than metastatic adenocarcinoma of the pancreas, reduce starting dose in patients with moderate to severe hepatic impairment. (2.4)
- Dose Reductions: Dose reductions or discontinuation may be needed based on severe hematologic, neurologic, cutaneous, or gastrointestinal toxicities. (2.5)
- Use caution when handling cytotoxic drugs. Closely monitor the infusion site for extravasation and infiltration. No premedication is required prior to administration. (2.6)

---------- DOSAGE FORMS AND STRENGTHS ----------

- For injectable suspension: lyophilized powder containing 100 mg of paclitaxel formulated as albumin-bound particles in single-use vial for reconstitution. (3)

---------- CONTRAINDICATIONS ----------

- Neutrophil counts of < 1,500 cells/mm^3. (4)
- Severe hypersensitivity reaction to ABRAXANE. (4)

---------- WARNINGS AND PRECAUTIONS ----------

- ABRAXANE causes myelosuppression. Monitor CBC and withhold and/or reduce the dose as needed. (5.1)
- Sensory neuropathy occurs frequently and may require dose reduction or treatment interruption. (5.2)
- Sepsis occurred in patients with or without neutropenia who received ABRAXANE in combination with gemcitabine; interrupt ABRAXANE and gemcitabine until sepsis resolves, and if neutropenia, until neutrophils are at least 1500 cells/mm^3, then resume treatment at reduced dose levels. (5.3)
- Pneumonitis occurred with the use of ABRAXANE in combination with gemcitabine; permanently discontinue treatment with ABRAXANE and gemcitabine. (5.4)
- Severe hypersensitivity reactions with fatal outcome have been reported. Do not re-challenge with this drug. (5.5)
- Exposure and toxicity of paclitaxel can be increased in patients with hepatic impairment; therefore administer with caution. (5.6)
- ABRAXANE contains albumin derived from human blood, which has a theoretical risk of viral transmission. (5.7)
- Fetal harm may occur when administered to a pregnant woman. Advise women of childbearing potential to avoid becoming pregnant while receiving ABRAXANE. (5.8)
- Advise men not to father a child while on ABRAXANE. (5.9)

---------- ADVERSE REACTIONS ----------

- The most common adverse reactions (≥ 20%) in metastatic breast cancer are alopecia, neutropenia, sensory neuropathy, abnormal ECG, fatigue/asthenia, myalgia/arthralgia, AST elevation, alkaline phosphatase elevation, anemia, nausea, infections, and diarrhea. (6.1)
- The most common adverse reactions (≥ 20%) in NSCLC are anemia, neutropenia, thrombocytopenia, alopecia, peripheral neuropathy, nausea, and fatigue. (6.2)
- The most common (≥ 20%) adverse reactions of ABRAXANE in adenocarcinoma of the pancreas are neutropenia, fatigue, peripheral neuropathy, nausea, alopecia, peripheral edema, diarrhea, pyrexia, vomiting, decreased appetite, rash, and dehydration. (6.3)

To report SUSPECTED ADVERSE REACTIONS, contact Celgene Corporation at 1-888-423-5436 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

---------- DRUG INTERACTIONS ----------

- Use caution when concomitantly administering ABRAXANE with inhibitors or inducers of either CYP2C8 or CYP3A4. (7)

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.

Revised: 12/2014

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*FULL PRESCRIBING INFORMATION: CONTENTS**

* Sections or subsections omitted from the Full Prescribing Information are not listed.

FULL PRESCRIBING INFORMATION
ABRAXANE® for Injectable Suspension (paclitaxel protein-bound particles for injectable suspension) (albumin-bound)

WARNING: NEUTROPENIA

- **Do not administer ABRAXANE therapy to patients who have baseline neutrophil counts of less than 1,500 cells/mm^3. In order to monitor the occurrence of bone marrow suppression, primarily neutropenia, which may be severe and result in infection, it is recommended that frequent peripheral blood cell counts be performed on all patients receiving ABRAXANE *[see Contraindications (4), Warnings and Precautions (5.1) and Adverse Reactions (6.1, 6.2, 6.3)]*.**
- **Note: An albumin form of paclitaxel may substantially affect a drug's functional properties relative to those of drug in solution. DO NOT SUBSTITUTE FOR OR WITH OTHER PACLITAXEL FORMULATIONS.**

1 INDICATIONS AND USAGE

1.1 Metastatic Breast Cancer
ABRAXANE is indicated for the treatment of breast cancer after failure of combination chemotherapy for metastatic disease or relapse within 6 months of adjuvant chemotherapy. Prior therapy should have included an anthracycline unless clinically contraindicated.

1.2 Non-Small Cell Lung Cancer
ABRAXANE is indicated for the first-line treatment of locally advanced or metastatic non-small cell lung cancer, in combination with carboplatin, in patients who are not candidates for curative surgery or radiation therapy.

1.3 Adenocarcinoma of the Pancreas
ABRAXANE is indicated for the first-line treatment of patients with metastatic adenocarcinoma of the pancreas, in combination with gemcitabine.

2 DOSAGE AND ADMINISTRATION

2.1 Metastatic Breast Cancer
After failure of combination chemotherapy for metastatic breast cancer or relapse within 6 months of adjuvant chemotherapy, the recommended regimen for ABRAXANE is 260 mg/m^2 administered intravenously over 30 minutes every 3 weeks.

2.2 Non-Small Cell Lung Cancer
The recommended dose of ABRAXANE is 100 mg/m^2 administered as an intravenous infusion over 30 minutes on Days 1, 8, and 15 of each 21-day cycle. Administer carboplatin on Day 1 of each 21 day cycle immediately after ABRAXANE *[see Clinical Studies (14.2)]*.

2.3 Adenocarcinoma of the Pancreas
The recommended dose of ABRAXANE is 125 mg/m^2 administered as an intravenous infusion over 30-40 minutes on Days 1, 8 and 15 of each 28-day cycle. Administer gemcitabine immediately after ABRAXANE on Days 1, 8 and 15 of each 28-day cycle *[see Clinical Studies (14.3)]*.

2.4 Dosage in Patients with Hepatic Impairment
For patients with mild hepatic impairment (total bilirubin greater than ULN and less than or equal to 1.5 x ULN and aspartate aminotransferase [AST] less than or equal to 10 x ULN), no dose adjustments are required, regardless of indication.

Do not administer ABRAXANE to patients with metastatic adenocarcinoma of the pancreas who have moderate to severe hepatic impairment.

Do not administer ABRAXANE to patients with total bilirubin greater than 5 x ULN or AST greater than 10 x ULN regardless of indication as these patients have not been studied.

Recommendations for dosage adjustment for the first course of therapy are shown in Table 1.

Table 1: Recommendations for Starting Dose in Patients with Hepatic Impairment

	SGOT (AST) Levels		Bilirubin Levels	ABRAXANE Dose[a]		
				MBC	NSCLC[c]	Pancreatic[c] Adenocarcinoma
Mild	< 10 x ULN	AND	> ULN to ≤ 1. 5 x ULN	260 mg/m^2	100 mg/m^2	125 mg/m^2
Moderate	< 10 x ULN	AND	> 1.5 to ≤ 3 x ULN	200 mg/m^2 [b]	80 mg/m^2 [b]	not recommended
Severe	< 10 x ULN	AND	> 3 to ≤ 5 x ULN	200 mg/m^2 [b]	80 mg/m^2 [b]	not recommended
	> 10 x ULN	OR	> 5 x ULN	not recommended	not recommended	not recommended

MBC = Metastatic Breast Cancer; NSCLC = Non-Small Cell Lung Cancer.
[a] Dosage recommendations are for the first course of therapy. The need for further dose adjustments in subsequent courses should be based on individual tolerance.
[b] A dose increase to 260 mg/m^2 for patients with metastatic breast cancer or 100 mg/m^2 for patients with non-small cell lung cancer in subsequent courses should be considered if the patient tolerates the reduced dose for two cycles.
[c] Patients with bilirubin levels above the upper limit of normal were excluded from clinical trials for pancreatic or lung cancer.

2.5 Dose Reduction/Discontinuation Recommendations

Metastatic Breast Cancer
Patients who experience severe neutropenia (neutrophils less than 500 cells/mm^3 for a week or longer) or severe sensory neuropathy during ABRAXANE therapy should have dosage reduced to 220 mg/m^2 for subsequent courses of ABRAXANE. For recurrence of severe neutropenia or severe sensory neuropathy, additional dose reduction should be made to 180 mg/m^2. For Grade 3 sensory neuropathy hold treatment until resolution to Grade 1 or 2, followed by a dose reduction for all subsequent courses of ABRAXANE *[see Contraindications (4), Warnings and Precautions (5.1, 5.2) and Adverse Reactions (6.1)]*.

Non-Small Cell Lung Cancer
- Do not administer ABRAXANE on Day 1 of a cycle until absolute neutrophil count (ANC) is at least 1500 cells/mm^3 and platelet count is at least 100,000 cells/mm^3 *[see Contraindications (4), Warnings and Precautions (5.1) and Adverse Reactions (6.2)]*.
- In patients who develop severe neutropenia or thrombocytopenia withhold treatment until counts recover to an absolute neutrophil count of at least 1500 cells/mm^3 and platelet count of at least 100,000 cells/mm^3 on Day 1 or to an absolute neutrophil count of at least 500 cells/mm^3 and platelet count of at least 50,000 cells/mm^3 on Days 8 or 15 of the cycle. Upon resumption of dosing, permanently reduce ABRAXANE and carboplatin doses as outlined in Table 2.
- Withhold ABRAXANE for Grade 3-4 peripheral neuropathy. Resume ABRAXANE and carboplatin at reduced doses (see Table 2) when peripheral neuropathy improves to Grade 1 or completely resolves *[see Warnings and Precautions (5.2) and Adverse Reactions (6.2)]*.

Table 2: Permanent Dose Reductions for Hematologic and Neurologic Adverse Drug Reactions in NSCLC

Adverse Drug Reaction	Occurrence	Weekly ABRAXANE Dose (mg/m^2)	Every 3-Week Carboplatin Dose (AUC mg•min/mL)
Neutropenic Fever (ANC less than 500/mm^3 with fever >38°C) OR Delay of next cycle by more than 7 days for ANC less than 1500/mm^3 OR ANC less than 500/mm^3 for more than 7 days	First	75	4.5
	Second	50	3
	Third	Discontinue Treatment	
Platelet count less than 50,000/mm^3	First	75	4.5
	Second	Discontinue Treatment	
Severe sensory Neuropathy – Grade 3 or 4	First	75	4.5
	Second	50	3
	Third	Discontinue Treatment	

Adenocarcinoma of the Pancreas
Dose level reductions for patients with adenocarcinoma of the pancreas, as referenced in Tables 4 and 5, are provided in Table 3.

Table 3: Dose Level Reductions for Patients with Adenocarcinoma of the Pancreas

Dose Level	ABRAXANE (mg/m^2)	Gemcitabine (mg/m^2)
Full dose	125	1000
1st dose reduction	100	800
2nd dose reduction	75	600
If additional dose reduction required	Discontinue	Discontinue

Recommended dose modifications for neutropenia and thrombocytopenia for patients with adenocarcinoma of the pancreas are provided in Table 4.

Table 4: Dose Recommendation and Modifications for Neutropenia and/or Thrombocytopenia at the Start of a Cycle or within a Cycle for Patients with Adenocarcinoma of the Pancreas

Cycle Day	ANC (cells/mm^3)		Platelet count (cells/mm^3)	ABRAXANE / Gemcitabine
Day 1	< 1500	OR	< 100,000	Delay doses until recovery
Day 8	500 to < 1000	OR	50,000 to < 75,000	Reduce 1 dose level
	< 500	OR	< 50,000	Withhold doses
Day 15: If Day 8 doses were reduced or given without modification:				
	500 to < 1000	OR	50,000 to < 75,000	Reduce 1 dose level from Day 8
	< 500	OR	< 50,000	Withhold doses
Day 15: If Day 8 doses were withheld:				
	≥ 1000	OR	≥ 75,000	Reduce 1 dose level from Day 1
	500 to < 1000	OR	50,000 to < 75,000	Reduce 2 dose levels from Day 1
	< 500	OR	< 50,000	Withhold doses

ANC = Absolute Neutrophil Count

Recommended dose modifications for other adverse drug reactions in patients with adenocarcinoma of the pancreas are provided in Table 5.

Table 5: Dose Modifications for Other Adverse Drug Reactions in Patients with Adenocarcinoma of the Pancreas

Adverse Drug Reaction	ABRAXANE	Gemcitabine
Febrile Neutropenia: Grade 3 or 4	Withhold until fever resolves and ANC ≥ 1500; resume at next lower dose level	
Peripheral Neuropathy: Grade 3 or 4	Withhold until improves to ≤ Grade 1; resume at next lower dose level	No dose reduction
Cutaneous Toxicity: Grade 2 or 3	Reduce to next lower dose level; discontinue treatment if toxicity persists	
Gastrointestinal Toxicity: Grade 3 mucositis or diarrhea	Withhold until improves to ≤ Grade 1; resume at next lower dose level	

2.6 Preparation and Administration Precautions
ABRAXANE is a cytotoxic drug and, as with other potentially toxic paclitaxel compounds, caution should be exercised in handling ABRAXANE. The use of gloves is recommended. If ABRAXANE (lyophilized cake or reconstituted suspension) contacts the skin, wash the skin immediately and thoroughly with soap and water. Following topical exposure to paclitaxel, events may include tingling, burning and redness. If ABRAXANE contacts mucous membranes, the membranes should be flushed thoroughly with water.

Given the possibility of extravasation, it is advisable to closely monitor the infusion site for possible infiltration during drug administration. Limiting the infusion of ABRAXANE to 30 minutes, as directed, reduces the likelihood of infusion-related reactions *[see Adverse Reactions (6.4)]*.

Premedication to prevent hypersensitivity reactions is generally not needed prior to the administration of ABRAXANE. Premedication may be needed in patients who have had prior hypersensitivity reactions to ABRAXANE. Patients who experience a severe hypersensitivity reaction to ABRAXANE should not be re-challenged with this drug [*see Warnings and Precautions (5.5)*].

2.7 Preparation for Intravenous Administration

ABRAXANE is supplied as a sterile lyophilized powder for reconstitution before use. **AVOID ERRORS, READ ENTIRE PREPARATION INSTRUCTIONS PRIOR TO RECONSTITUTION.**

1. Aseptically, reconstitute each vial by injecting 20 mL of 0.9% Sodium Chloride Injection, USP.
2. Slowly inject the 20 mL of 0.9% Sodium Chloride Injection, USP, over a minimum of 1 minute, using the sterile syringe to direct the solution flow onto the INSIDE WALL OF THE VIAL.

3. DO NOT INJECT the 0.9% Sodium Chloride Injection, USP, directly onto the lyophilized cake as this will result in foaming.
4. Once the injection is complete, allow the vial to sit for a minimum of 5 minutes to ensure proper wetting of the lyophilized cake/powder.
5. Gently swirl and/or invert the vial slowly for at least 2 minutes until complete dissolution of any cake/powder occurs. Avoid generation of foam.
6. If foaming or clumping occurs, stand solution for at least 15 minutes until foam subsides.

Each mL of the reconstituted formulation will contain 5 mg/mL paclitaxel.

Calculate the exact total dosing volume of 5 mg/mL suspension required for the patient: Dosing volume (mL) = Total dose (mg)/5 (mg/mL).

The reconstituted suspension should be milky and homogenous without visible particulates. If particulates or settling are visible, the vial should be **gently** inverted again to ensure complete resuspension prior to use. Discard the reconstituted suspension if precipitates are observed. Discard any unused portion.

Inject the appropriate amount of reconstituted ABRAXANE into an empty, sterile intravenous bag [plasticized polyvinyl chloride (PVC) containers, PVC or non-PVC type intravenous bag]. The use of specialized DEHP-free solution containers or administration sets is not necessary to prepare or administer ABRAXANE infusions. The use of an in-line filter is not recommended.

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration whenever solution and container permit.

2.8 Stability

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

Stability of Reconstituted Suspension in the Vial

Reconstituted ABRAXANE in the vial should be used immediately, but may be refrigerated at 2ºC to 8ºC (36ºF to 46ºF) for a maximum of 24 hours if necessary. If not used immediately, each vial of reconstituted suspension should be replaced in the original carton to protect it from bright light. Discard any unused portion.

Stability of Reconstituted Suspension in the Infusion Bag

The suspension for infusion when prepared as recommended in an infusion bag should be used immediately, but may be refrigerated at 2°C to 8°C (36°F to 46°F) and protected from bright light for a maximum of 24 hours.

The total combined refrigerated storage time of reconstituted ABRAXANE in the vial and in the infusion bag is 24 hours. This may be followed by storage in the infusion bag at ambient temperature (approximately 25°C) and lighting conditions for a maximum of 4 hours.

Discard any unused portion.

The following common (≥ 10% incidence) adverse reactions were observed at a similar incidence in ABRAXANE plus carboplatin-treated and paclitaxel injection plus carboplatin-treated patients: alopecia 56%, nausea 27%, fatigue 25%, decreased appetite 17%, asthenia 16%, constipation 16%, diarrhea 15%, vomiting 12%, dyspnea 12%, and rash 10% (incidence rates are for the ABRAXANE plus carboplatin treatment group).

Table 7 provides the frequency and severity of laboratory-detected abnormalities which occurred with a difference of ≥ 5% for all grades (1-4) or ≥ 2% for Grade 3-4 toxicity between ABRAXANE plus carboplatin-treated patients or paclitaxel injection plus carboplatin-treated patients.

Table 7: Selected Hematologic Laboratory-Detected Abnormalities With a Difference of ≥ 5% for grades (1-4) or ≥ 2% for Grade 3-4 Toxicity Between Treatment Groups

	ABRAXANE (100 mg/m^2 weekly) plus carboplatin		Paclitaxel Injection (200 mg/m^2 every 3 weeks) plus carboplatin	
	Grades 1-4 (%)	Grade 3-4 (%)	Grades 1-4 (%)	Grade 3-4 (%)
Anemia[1,2]	98	28	91	7
Neutropenia[1,3]	85	47	83	58
Thrombocytopenia[1,3]	68	18	55	9

[1] 508 patients assessed in ABRAXANE/carboplatin-treated group
[2] 514 patients assessed in paclitaxel injection/carboplatin-treated group
[3] 513 patients assessed in paclitaxel injection/carboplatin-treated group

Table 8 provides the frequency and severity of adverse reactions, which occurred with a difference of ≥ 5% for all grades (1-4) or ≥ 2% for Grade 3-4 between either treatment group for the 514 ABRAXANE plus carboplatin-treated patients compared with the 524 patients who received paclitaxel injection plus carboplatin.

Table 8: Selected Adverse Reactions with a Difference of ≥5% for All Grade Toxicity or ≥2% for Grade 3-4 Toxicity Between Treatment Groups

System Organ Class	MedDRA v 12.1 Preferred Term	ABRAXANE (100 mg/m^2 weekly) + carboplatin (N=514)		Paclitaxel Injection (200 mg/m^2 every 3 weeks) + carboplatin (N=524)	
		Grade 1-4 Toxicity (%)	Grade 3-4 Toxicity (%)	Grades 1-4 Toxicity (%)	Grade 3-4 Toxicity (%)
Nervous system disorders	Peripheral neuropathy[a]	48	3	64	12
General disorders and administration site conditions	Edema peripheral	10	0	4	<1
Respiratory thoracic and mediastinal disorders	Epistaxis	7	0	2	0
Musculoskeletal and connective tissue disorders	Arthralgia	13	<1	25	2
	Myalgia	10	<1	19	2

[a] Peripheral neuropathy is defined by the MedDRA Version 14.0 SMQ neuropathy (broad scope).

For the ABRAXANE plus carboplatin treated group, 17/514 (3%) patients developed Grade 3 peripheral neuropathy and no patients developed Grade 4 peripheral neuropathy. Grade 3 neuropathy improved to Grade 1 or resolved in 10/17 patients (59%) following interruption or discontinuation of ABRAXANE.

6.3 Clinical Trials Experience in Adenocarcinoma of the Pancreas

Adverse reactions were assessed in 421 patients who received ABRAXANE plus gemcitabine and 402 patients who received gemcitabine for the first-line systemic treatment of metastatic adenocarcinoma of the pancreas in a multicenter, multinational, randomized, controlled, open-label trial. Patients received a median treatment duration of 3.9 months in the ABRAXANE/gemcitabine group and 2.8 months in the gemcitabine group. For the treated population, the median relative dose intensity for gemcitabine was 75% in the ABRAXANE/gemcitabine group and 85% in the gemcitabine group. The median relative dose intensity of ABRAXANE was 81%.

Table 9 provides the frequency and severity of laboratory-detected abnormalities which occurred at a higher incidence for Grades 1-4 (≥ 5%) or for Grade 3-4 (≥ 2%) toxicity in ABRAXANE plus gemcitabine-treated patients.

Table 9: Selected Hematologic Laboratory-Detected Abnormalities with a Higher Incidence (≥ 5% for Grades 1-4 or ≥ 2% for Grades 3-4 Events) in the ABRAXANE/Gemcitabine Arm

	ABRAXANE(125 mg/m^2)/ Gemcitabine[d]		Gemcitabine	
	Grades 1-4 (%)	Grade 3-4 (%)	Grades 1-4 (%)	Grade 3-4 (%)
Neutropenia[a,b]	73	38	58	27
Thrombocytopenia[b,c]	74	13	70	9

[a] 405 patients assessed in ABRAXANE/gemcitabine-treated group
[b] 388 patients assessed in gemcitabine-treated group
[c] 404 patients assessed in ABRAXANE/gemcitabine-treated group
[d] Neutrophil growth factors were administered to 26% of patients in the ABRAXANE/gemcitabine group.

Table 10 provides the frequency and severity of adverse reactions which occurred with a difference of ≥ 5% for all grades or ≥ 2% for Grade 3 or higher in the ABRAXANE plus gemcitabine-treated group compared to the gemcitabine group.

Table 10: Selected Adverse Reactions with a Higher Incidence (≥5% for All Grade Toxicity or ≥2% for Grade 3 or Higher Toxicity) in the ABRAXANE/Gemcitabine Arm

System Organ Class	Adverse Reaction	ABRAXANE (125 mg/m^2) and gemcitabine (N=421)		Gemcitabine (N=402)	
		All Grades	Grade 3 or Higher	All Grades	Grade 3 or Higher
General disorders and administration site conditions	Fatigue	248 (59%)	77 (18%)	183 (46%)	37 (9%)
	Peripheral edema	194 (46%)	13 (3%)	122 (30%)	12 (3%)
	Pyrexia	171 (41%)	12 (3%)	114 (28%)	4 (1%)
	Asthenia	79 (19%)	29 (7%)	54 (13%)	17 (4%)
	Mucositis	42 (10%)	6 (1%)	16 (4%)	1 (<1%)
Gastrointestinal disorders	Nausea	228 (54%)	27 (6%)	192 (48%)	14 (3%)
	Diarrhea	184 (44%)	26 (6%)	95 (24%)	6 (1%)
	Vomiting	151 (36%)	25 (6%)	113 (28%)	15 (4%)
Skin and subcutaneous tissue disorders	Alopecia	212 (50%)	6 (1%)	21 (5%)	0
	Rash	128 (30%)	8 (2%)	45 (11%)	2 (<1%)
Nervous system disorders	Peripheral neuropathy[a]	227 (54%)	70 (17%)	51 (13%)	3 (1%)
	Dysgeusia	68 (16%)	0	33 (8%)	0
	Headache	60 (14%)	1 (<1%)	38 (9%)	1 (<1%)
Metabolism and nutrition disorders	Decreased appetite	152 (36%)	23 (5%)	104 (26%)	8 (2%)
	Dehydration	87 (21%)	31 (7%)	45 (11%)	10 (2%)
	Hypokalemia	52 (12%)	18 (4%)	28 (7%)	6 (1%)
Respiratory, thoracic and mediastinal disorders	Cough	72 (17%)	0	30 (7%)	0
	Epistaxis	64 (15%)	1 (<1%)	14 (3%)	1 (<1%)
Infections and infestations	Urinary tract infections[b]	47 (11%)	10 (2%)	20 (5%)	1 (<1%)
Musculoskeletal and connective tissue disorders	Pain in extremity	48 (11%)	3 (1%)	24 (6%)	3 (1%)
	Arthralgia	47 (11%)	3 (1%)	13 (3%)	1 (<1%)
	Myalgia	44 (10%)	4 (1%)	15 (4%)	0

Table 10: Selected Adverse Reactions with a Higher Incidence (≥5% for All Grade Toxicity or ≥2% for Grade 3 or Higher Toxicity) in the ABRAXANE/Gemcitabine Arm (continued)

System Organ Class	Adverse Reaction	ABRAXANE (125 mg/m^2) and gemcitabine (N=421)		Gemcitabine (N=402)	
		All Grades	Grade 3 or Higher	All Grades	Grade 3 or Higher
Psychiatric disorders	Depression	51 (12%)	1 (<1%)	24 (6%)	0

[a] Peripheral neuropathy is defined by the MedDRA Version 15.0 Standard MedDRA Query neuropathy (broad scope).
[b] Urinary tract infections includes the preferred terms of: urinary tract infection, cystitis, urosepsis, urinary tract infection bacterial, and urinary tract infection enterococcal.

Additional clinically relevant adverse reactions that were reported in < 10% of the patients with adenocarcinoma of the pancreas who received ABRAXANE/gemcitabine included:

Infections & infestations: oral candidiasis, pneumonia
Vascular disorders: hypertension
Cardiac disorders: tachycardia, congestive cardiac failure
Eye disorders: cystoid macular edema

Peripheral Neuropathy
Grade 3 peripheral neuropathy occurred in 17% of patients who received ABRAXANE/gemcitabine compared to 1% of patients who received gemcitabine only; no patients developed grade 4 peripheral neuropathy. The median time to first occurrence of Grade 3 peripheral neuropathy in the ABRAXANE arm was 140 days. Upon suspension of ABRAXANE dosing, the median time to improvement from Grade 3 peripheral neuropathy to ≤ Grade 1 was 29 days. Of ABRAXANE-treated patients with Grade 3 peripheral neuropathy, 44% resumed ABRAXANE at a reduced dose.

Sepsis
Sepsis occurred in 5% of patients who received ABRAXANE/gemcitabine compared to 2% of patients who received gemcitabine alone. Sepsis occurred both in patients with and without neutropenia. Risk factors for sepsis included biliary obstruction or presence of biliary stent.

Pneumonitis
Pneumonitis occurred in 4% of patients who received ABRAXANE/gemcitabine compared to 1% of patients who received gemcitabine alone. Two of 17 patients in the ABRAXANE arm with pneumonitis died.

6.4 Post-Marketing Experience with ABRAXANE and other Paclitaxel Formulations
Unless otherwise noted, the following discussion refers to the adverse reactions that have been identified during post-approval use of ABRAXANE. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure. In some instances, severe events observed with paclitaxel injection may be expected to occur with ABRAXANE.

Hypersensitivity Reactions
Severe and sometimes fatal hypersensitivity reactions have been reported with ABRAXANE. The use of ABRAXANE in patients previously exhibiting hypersensitivity to paclitaxel injection or human albumin has not been studied.

Cardiovascular
There have been reports of congestive heart failure, left ventricular dysfunction, and atrioventricular block with ABRAXANE. Most of the individuals were previously exposed to cardiotoxic drugs, such as anthracyclines, or had underlying cardiac history.

Respiratory
There have been reports of pneumonitis, interstitial pneumonia and pulmonary embolism in patients receiving ABRAXANE and reports of radiation pneumonitis in patients receiving concurrent radiotherapy. Reports of lung fibrosis have been received as part of the continuing surveillance of paclitaxel injection safety and may also be observed with ABRAXANE.

Neurologic
Cranial nerve palsies and vocal cord paresis have been reported, as well as autonomic neuropathy resulting in paralytic ileus.

Vision Disorders
Reports in the literature of abnormal visual evoked potentials in patients treated with paclitaxel injection suggest persistent optic nerve damage. These may also be observed with ABRAXANE.

Reduced visual acuity due to cystoid macular edema (CME) has been reported during treatment with ABRAXANE as well as with other taxanes. After cessation of treatment, CME improves and visual acuity may return to baseline.

Hepatic
Reports of hepatic necrosis and hepatic encephalopathy leading to death have been received as part of the continuing surveillance of paclitaxel injection safety and may occur following ABRAXANE treatment.

Gastrointestinal (GI)
There have been reports of intestinal obstruction, intestinal perforation, pancreatitis, and ischemic colitis following ABRAXANE treatment. There have been reports of neutropenic enterocolitis (typhlitis), despite the coadministration of G-CSF, occurring in patients treated with paclitaxel injection alone and in combination with other chemotherapeutic agents.

Injection Site Reaction
There have been reports of extravasation of ABRAXANE. Given the possibility of extravasation, it is advisable to monitor closely the ABRAXANE infusion site for possible infiltration during drug administration.

Severe events such as phlebitis, cellulitis, induration, necrosis, and fibrosis have been reported as part of the continuing surveillance of paclitaxel injection safety. In some cases the onset of the injection site reaction in paclitaxel injection patients either occurred during a prolonged infusion or was delayed by a week to ten days. Recurrence of skin reactions at a site of previous extravasation following administration of paclitaxel injection at a different site, i.e., "recall", has been reported.

Other Clinical Events
Skin reactions including generalized or maculopapular rash, erythema, and pruritus have been observed with ABRAXANE. There have been case reports of photosensitivity reactions, radiation recall phenomenon, and in some patients previously exposed to capecitabine, reports of palmar-plantar erythrodysesthesia. Stevens-Johnson syndrome and toxic epidermal necrolysis have been reported.

There have been reports of conjunctivitis, cellulitis, and increased lacrimation with paclitaxel injection.

6.5 Accidental Exposure
No reports of accidental exposure to ABRAXANE have been received. However, upon inhalation of paclitaxel, dyspnea, chest pain, burning eyes, sore throat, and nausea have been reported. Following topical exposure, events have included tingling, burning, and redness.

7 DRUG INTERACTIONS
The metabolism of paclitaxel is catalyzed by CYP2C8 and CYP3A4. Caution should be exercised when administering ABRAXANE concomitantly with medicines known to inhibit (e.g., ketoconazole and other imidazole antifungals, erythromycin, fluoxetine, gemfibrozil, cimetidine, ritonavir, saquinavir, indinavir, and nelfinavir) or induce (e.g., rifampicin, carbamazepine, phenytoin, efavirenz, and nevirapine) either CYP2C8 or CYP3A4.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy
Pregnancy Category D *[see Warnings and Precautions (5.8)]*.

There are no adequate and well-controlled studies in pregnant women using ABRAXANE. Based on its mechanism of action and findings in animals, ABRAXANE can cause fetal harm when administered to a pregnant woman. If this drug is used during pregnancy, or if the patient becomes pregnant while receiving this drug, the patient should be apprised of the potential hazard to the fetus. Women of childbearing potential should be advised to avoid becoming pregnant while receiving ABRAXANE.

Administration of paclitaxel formulated as albumin-bound particles to rats during pregnancy, on gestation days 7 to 17 at doses of 6 mg/m^2 (approximately 2% of the daily maximum recommended human dose on a mg/m^2 basis) caused embryofetal toxicities, as indicated by intrauterine mortality, increased resorptions (up to 5-fold), reduced numbers of litters and live fetuses, reduction in fetal body weight and increase in fetal anomalies. Fetal anomalies included soft tissue and skeletal malformations, such as eye bulge, folded retina, microphthalmia, and dilation of brain ventricles. A lower incidence of soft tissue and skeletal malformations were also exhibited at 3 mg/m^2 (approximately 1% of the daily maximum recommended human dose on a mg/m^2 basis).

8.3 Nursing Mothers
It is not known whether paclitaxel is excreted in human milk. Paclitaxel and/or its metabolites were excreted into the milk of lactating rats. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants, a decision should be made to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

8.4 Pediatric Use
The safety and effectiveness of ABRAXANE in pediatric patients have not been evaluated.

8.5 Geriatric Use
Of the 229 patients in the randomized study who received ABRAXANE for the treatment of metastatic breast cancer, 13% were at least 65 years of age and < 2% were 75 years or older. No toxicities occurred notably more frequently among patients who received ABRAXANE.

Of the 514 patients in the randomized study who received ABRAXANE and carboplatin for the first-line treatment of non-small cell lung cancer, 31% were 65 years or older and 3.5% were 75 years or older. Myelosuppression, peripheral neuropathy, and arthralgia were more frequent in patients 65 years or older compared to patients younger than 65 years old. No overall difference in effectiveness, as measured by response rates, was observed between patients 65 years or older compared to patients younger than 65 years old.

13.7 APPENDIX G INVESTIGATOR AGREEMENT AND SIGNATURE PAGE

Protocol Title: *A Multicenter Randomized Phase II Study of NPC-1C in Combination with Gemcitabine and nab-Paclitaxel versus Gemcitabine and nab-Paclitaxel alone in Patients with Metastatic or Locally Advanced Pancreatic Cancer Previously Treated with FOLFIRINOX*

Study drug: NPC-1C (NEO-102)

Protocol Number: **Precision Biologics-1201 (PB-1201)**

Edition Number: 13

I have read the Protocol, and I agree to conduct the study as detailed herein and in compliance with ICH Guidelines for Good Clinical Practice and applicable regulatory requirements and to inform all who assist me in the conduct of this study of their responsibilities and obligations.

_____

Principal Investigator (printed name)

_____ _____

Principal Investigator (signature) Date

_____

_____

_____

Investigational site or name of institution and location (printed)