ALLIANCE FOR CLINICAL TRIALS IN ONCOLOGY

ALLIANCE A022106

PHASE II/III SECOND-LINE NABPLAGEM VS. NAB-PACLITAXEL/GEMCITABINE IN *BRCA1/2* OR *PALB2* MUTANT METASTATIC PANCREATIC DUCTAL ADENOCARCINOMA (PLATINUM)

Commercial agent(s): Nab-paclitaxel (NSC #736631); Cisplatin (NSC #119875; Gemcitabine (NSC #613327)

ClinicalTrials.gov Identifier: NCTXXXXXX

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Study Resources:

Expedited Adverse Event Reporting **https://ctepcore.nci.nih.gov/ctepaers/**	**Medidata Rave® iMedidata portal** https://login.imedidata.com
OPEN (Oncology Patient Enrollment Network) https://open.ctsu.org	**Biospecimen Management System** http://bioms.allianceforclinicaltrialsinoncology.org

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Protocol-related questions may be directed as follows:	
Questions	**Contact (via email)**
Questions regarding patient eligibility, treatment, and dose modification:	Study Chair, Nursing Contact, and (where applicable) Data Manager
Questions related to data submission, RAVE or patient follow-up:	Data Manager
Questions regarding the protocol document and model informed consent:	Protocol Coordinator
Questions related to IRB review	Alliance Regulatory Inbox regulatory@allianceNCTN.org
Questions regarding CTEP-AERS reporting:	Alliance Pharmacovigilance Inbox pharmacovigilance@alliancenctn.org
Questions regarding specimens/specimen submissions:	Alliance Biorepository at Ohio State University
Questions regarding drug administration	Pharmacy Contact

CANCER TRIALS SUPPORT UNIT (CTSU) ADDRESS AND CONTACT INFORMATION

For regulatory requirements:	**For patient enrollments:**	**For data submission:**
Regulatory documentation must be submitted to the Cancer Trials Support Unit (CTSU) via the Regulatory Submission Portal. (Sign in at https://www.ctsu.org, and select the Regulatory > Regulatory Submission.) Institutions with patients waiting that are unable to use the Portal should alert the CTSU Regulatory Office immediately by phone or email: 1-866-651-CTSU (2878) or CTSURegHelp@coccg.org to receive further instruction and support. Contact the CTSU Regulatory Help Desk at 1-866-651-CTSU (2878) or CTSURegHelp@coccg.org for regulatory assistance.	Refer to the patient enrollment section of the protocol for instructions on using the Oncology Patient Enrollment Network (OPEN). OPEN is accessed at https://www.ctsu.org/OPEN_SYSTEM/ or https://OPEN.ctsu.org. Contact the CTSU Help Desk with any OPEN-related questions by phone or email: 1-888-823-5923, or ctsucontact@westat.com.	Data collection for this study will be done exclusively through Medidata Rave. Refer to the data submission section of the protocol for further instructions.
The most current version of the **study protocol and all supporting documents** must be downloaded from the protocol-specific page located on the CTSU members' website (https://www.ctsu.org). Permission to view and download this protocol and its supporting documents is restricted and is based on person and site roster assignment housed in the Roster Maintenance application and in most cases viewable and manageable via the Roster Update Management System (RUMS) on the CTSU members' website.		
<u>For clinical questions (i.e., patient eligibility or treatment-related)</u> see the Protocol Contacts, Page 2.		
<u>For non-clinical questions (i.e., unrelated to patient eligibility, treatment, or clinical data submission)</u> contact the CTSU Help Desk by phone or email: CTSU General Information Line – 1-888-823-5923, or ctsucontact@westat.com. All calls and correspondence will be triaged to the appropriate CTSU representative.		

PHASE II/III SECOND-LINE NABPLAGEM VS. NAB-PACLITAXEL/GEMCITABINE IN *BRCA1/2* OR *PALB2* MUTANT METASTATIC PANCREATIC DUCTAL ADENOCARCINOMA (PLATINUM)

Registration Eligibility Criteria (See Section 3.2)

-Histologic documentation of metastatic pancreatic adenocarcinoma, adenosquamous carcinoma, carcinoma or acinar carcinoma
-Pathogenic BRCA1/2 or PALB2 mutation (somatic or germline)
-Measurable disease by RECIST 1.1 criteria
-Potential trial participants should have recovered from clinically significant adverse events of their most recent therapy/intervention prior to enrollment
-Clinical or radiographic progression on first-line FOLFIRINOX (see §3.2.5)
-No prior Cisplatin (See §3.2.6)
-Age ≥ 18 years
-ECOG Performance Status 0-2
-Not pregnant and not nursing (see §3.2.10)
-Not greater than grade 2 peripheral sensory neuropathy
-For patients with a prior or concurrent malignancy (see §3.2.12)
-Patients with treated brain metastases are eligible (see §3.2.13)
-Patients with known HIV are eligible (see §3.2.14)
-Patients with known Hepatitis are eligible (see §3.2.15)
-No treatment with concomitant medications is not allowed (see §3.2.16)

Required Initial Laboratory Values

ANC	≥ 1500/mm^3
Hgb	≥ 8 g/dL
Platelet count:	≥ 100,000/mm^3
Creatinine:	≤ 1.8 x upper limit of normal (ULN)
Calc. creatinine clearance:	≥ 40 mL/min
Total bilirubin:	≤ 2.0 x ULN
AST/ALT:	≤ 3 x ULN or ≤5 x ULN if no liver metastases (as long as bilirubin within normal range)

Schema

1 Cycle = 28 Days

Registration/ Randomization 1:1

Arm 1: Nab-paclitaxel 100 mg/m^2 + cisplatin 25 mg/m^2 + gemcitabine 800 mg/m^2 on days 1 and 15

Arm 2: Nab-paclitaxel 125 mg/m^2 + gemcitabine 1000 mg/m^2 on days 1 and 15

Treatment is to continue until disease progression or unacceptable adverse event. Patients will be followed for 2 years from the end of treatment or until death, whichever comes first.

Please refer to the full protocol text for a complete description of the eligibility criteria and treatment plan.

Chemotherapy will be conducted at the registering institution. Laboratory tests may be performed at a non-registering institution.

If the Group credited for enrollment is a non-Alliance Group, then other requirements from the credited Group may apply.

Table of Contents

1.0 BACKGROUND

1.1 Pancreatic ductal adenocarcinoma

Pancreatic ductal adenocarcinoma (PDAC) remains a leading cause of cancer-related mortality, with a 5-year survival rate of 10%. One subgroup of particular interest is comprised of patients with homologous recombination (HR)-deficient tumors, which make up about 15-20% of all PDAC cases. For patients with HR-deficient PDAC and specifically *BRCA1/2 or PALB2* mutations, there is growing evidence to support using platinum-based therapies [1,2].

It is unknown whether the selection of platinum agent makes a difference in HR-deficient PDAC. Oxaliplatin represents the most commonly used platinum analogue for PDAC based on positive results from the phase III FOLFIRINOX trial. However, mechanistically oxaliplatin and cisplatin act on cancer cells very differently [3], a fact that is reflected in their disparate toxicity profiles and target diseases. Preclinical data from the laboratory of Kenneth Olive (Columbia University, New York) indicates that a genetically engineered, *Brca2* null murine model of pancreatic cancer responds potently to monotherapy cisplatin but exhibits no response to monotherapy oxaliplatin at twice the molar dose (K. Olive, personal communication). The Olive lab further ascribed the molecular mechanism of cisplatin to its enhanced ability to induce tumor-cell specific endoreplication specifically in *Brca2* null pancreatic tumor cells, leading to giant cell formation and mitotic catastrophe both *in vivo* and in cell culture experiments. By contrast, oxaliplatin had minimal effect on endoreduplication. This provides a molecular basis for utilizing cisplatin in the treatment of HDR-deficient pancreatic tumors.

A recently published phase II trial using gemcitabine and cisplatin as the chemotherapy backbone in PDAC patients with germline *BRCA* or *PALB2* mutations showed an objective response rate of close to 70% with a median PFS of 10 months [4]. These findings compare favorably to the efficacy outcomes reported in the pivotal phase III trials of FOLFIRINOX and gemcitabine plus nab-paclitaxel for non-biomarker-selected patients with advanced PDAC [5,6]. The NCCN guidelines also recommend considering gemcitabine and cisplatin as an alternative to FOLFIRINOX for patients with HR-deficient PDAC [7].

Meanwhile, a phase Ib/II trial by Jameson and colleagues evaluated a 3-drug regimen consisting of the combination of nab-paclitaxel, cisplatin, and gemcitabine (NABPLAGEM) in a non-biomarker-selected cohort of patients with untreated metastatic PDAC [8]. The response rate was 71%, with two complete responses (8%). Recognizing the small sample size (n=25), the promising clinical activity associated with this combination clearly warrants further investigation, both beyond the front-line setting and in subgroups of patients (such as the HRD subgroup) who would likely derive the greatest benefit.

For patients who receive first-line FOLFIRINOX and remain candidates for further treatment, a switch to gemcitabine-based chemotherapy, commonly the combination of gemcitabine/nab-paclitaxel, represents standard practice. However, given the benefit of platinum-based therapies for the subgroup of patients with *BRCA1/2* or *PALB2* mutant PDAC, we hypothesize that using a different regimen in the second-line setting which continues to include a (different) platinum analogue (cisplatin) represents a feasible and potentially more effective therapeutic strategy. We will test this hypothesis in the current phase II/III protocol, in which patients with *BRCA1/2* or *PALB2* mutant PDAC who have progressed on front-line FOLFIRINOX will be randomized to receive one of the following 2 treatment arms: NABPLAGEM or gemcitabine/nab-paclitaxel.

1.2 Evidence supporting the use of platinum-based therapies in HR

Pishvaian et *al*. evaluated a cohort of 820 pancreatic cancer patients in the national Know Your Tumor registry, demonstrating that longer overall survival was associated with platinum-based treatment among patients with HR-deficient tumors (defined as one of 21 mutations) [1]. In

another retrospective analysis from Memorial Sloan-Kettering of 262 patients, Park and colleagues reported that those with pathogenic HR-deficient PDAC (defined as one of 17 alterations) demonstrated longer progression-free survival (PFS) and OS, compared to patients without HR-deficiency, when treated with first-line platinum therapy [2].

1.3 Evidence supporting front-line gemcitabine/cisplatin as an option for patients with HR-deficient PDAC

A recently published phase II trial using gemcitabine and cisplatin as the chemotherapy backbone in PDAC patients with germline *BRCA* or *PALB2* mutations showed an objective response rate of close to 70% with a median PFS of 10 months [4]. These findings compare favorably to the efficacy outcomes reported in the pivotal phase III trials of FOLFIRINOX and gemcitabine plus nab-paclitaxel for non-biomarker-selected patients with advanced PDAC [5,6]. Recently published retrospective data for patients with germline or somatic *BRCA1/2* alterations further confirms longer survival for those treated with front-line platinum, with a markedly prolonged response among those with biallelic mutations [9]. The NCCN guidelines also recommend considering gemcitabine and cisplatin as an alternative to FOLFIRINOX for patients with HR-deficient PDAC [10].

1.4 Novel triplet combination of nab-paclitaxel, cisplatin, and gemcitabine

A recent phase Ib/II trial by Jameson and colleagues evaluated the combination of nab-paclitaxel, cisplatin, and gemcitabine (NABPLAGEM) in a non-biomarker-selected cohort of patients with untreated metastatic PDAC [8]. The maximum tolerated dose of cisplatin was 25 mg/m^2 with standard doses of gemcitabine (1,000 mg/m^2) and nab-paclitaxel (125 mg/m^2) on a 2-week-on, 1-week-off schedule. The response rate was 71%, with two complete responses (8%).

As we anticipate myelosuppression in this pre-treated patient population to be an issue, therefore, we will be using attenuated doses similar to the SWOG 1815 trial in biliary cancer (NCT03768414), specifically: cisplatin 25 mg/m^2, gemcitabine 800 mg/m^2, and nab-paclitaxel 100 mg/m^2, and treating on an every-other-week dose schedule (days 1 and 15 of a 28-day cycle), which aligns well with the biweekly dosing schedule of the control arm. Moreover, we have been collecting clinical data from a UCSF registry study evaluating NABPLAGEM in metastatic PDAC patients (n=9 subjects thus far), and have demonstrated the safety and feasibility of this regimen in the second line (and beyond) setting for this non-biomarker-selected cohort (unpublished data).

1.5 Rationale for Trial Design

The significance and rationale of this trial is based on the following principles: 1) there is an urgent need to improve and refine our treatment approach in patients with HR-deficient PDAC following front-line chemotherapy with FOLFIRINOX, 2) HR-deficient PDAC may derive additional benefit from continuing with platinum-based therapy in the second-line setting, and 3) correlative studies in this prospective setting, including whole genome and transcriptome sequencing, will help identify patients with HR-deficient PDAC who are most likely to benefit from a platinum-based strategy. There remains clinical equipoise regarding the optimal second-line regimen in this subgroup of patients. While there is evidence for platinum response in HR-deficient PDAC, *BRCA1/2* and *PALB2* mutations comprise the majority of cases, so eligibility will be limited to these mutations to be better able to interpret study results. With the primary endpoint of overall response rate (for the phase II portion) and overall survival (for the phase III portion), the results from this proposed study would identify a specific treatment arm that could be used to obtain NCCN designation as an appropriate option in the second line setting for this patient population.

2.0 OBJECTIVES

2.1 Primary objectives

2.1.1 **Phase II:** To evaluate and compare overall response rate (ORR) in patients with *BRCA1/2* or *PALB2* mutant pancreas cancer whose disease has progressed on front-line FOLFIRINOX treated with NABPLAGEM = nab-paclitaxel, gemcitabine, and cisplatin (arm 1) versus nab-paclitaxel and gemcitabine (arm 2).

2.1.2 **Phase III:** To evaluate and compare overall survival (OS) time in patients with *BRCA1/2* or *PALB2* mutant whose disease has progressed on front-line FOLFIRINOX treated with 1) NABPLAGEM = nab-paclitaxel, gemcitabine, and cisplatin (arm 1) versus nab-paclitaxel and gemcitabine (arm 2).

2.2 Secondary objective(s)

2.2.1 To evaluate and compare progression-free survival (PFS) per RECIST 1.1 criteria between 2 treatment arms.

2.2.2 To evaluate and compare duration of response (DoR) between 2 treatment arms.

2.2.3 To evaluate and compare CA19-9 response (defined as patients with a baseline CA19-9 ≥ 2x ULN who demonstrate a minimum 25% decrease in CA19-9 at any time point) between 2 treatment arms.

2.2.4 To evaluate and compare toxicity profile as assessed by treating clinicians between 2 treatment arms.

3.0 PATIENT SELECTION

For questions regarding eligibility criteria, see the Study Resources page. Please note that the Study Chair cannot grant waivers to eligibility requirements.

3.1 On-Study Guidelines

This clinical trial can fulfill its objectives only if patients appropriate for this trial are enrolled. All relevant medical and other considerations should be taken into account when deciding whether this protocol is appropriate for a particular patient. Clinicians should use their clinical judgement and have discussions with potential trial participants to assess their ability to follow protocol requirements safely.

Women and men of reproductive potential should agree to use an appropriate method of birth control throughout their participation in this study due to the teratogenic potential of the therapy utilized in this trial. Appropriate methods of birth control include abstinence, oral contraceptives, implantable hormonal contraceptives or double barrier method (diaphragm plus condom).

3.2 Eligibility Criteria

Use the spaces provided to confirm a patient's eligibility by indicating Yes or No as appropriate. It is not required to complete or submit the following page(s).

When calculating days of tests and measurements, the day a test or measurement is done is considered Day 0. Therefore, if a test were done on a Monday, the Monday one week later would be considered Day 7.

A female of childbearing potential is a sexually mature female who: 1) has not undergone a hysterectomy or bilateral oophorectomy; or 2) has not been naturally postmenopausal for at least 12 consecutive months (i.e., has had menses at any time in the preceding 12 consecutive months).

___ **3.2.1 Documentation of Disease**

Metastatic pancreatic adenocarcinoma. Adenosquamous carcinoma, squamous carcinoma, acinar cell carcinoma, and carcinoma not otherwise specified are also acceptable.

___ **3.2.2 BRCA1/2 or PALB2 testing**

BRCA1/2 or PALB2 mutation (somatic or germline) identified on any CLIA-certified gene panel. Mutations must be considered pathogenic or likely pathogenic by a reference database such as ClinVar or OncoKb.org. (Submission of mutation report will be required, see section 6.1.4)

___ **3.2.3** Measurable disease as defined in Section 11.0.

___ **3.2.4** Potential trial participants should have recovered from clinically significant adverse events of their most recent therapy/intervention prior to enrollment.

___ **3.2.5 Clinical or radiographic progression on first-line FOLFIRINOX (or NALIRIFOX) for metastatic disease.**

- Patients whose front-line chemotherapy was required to be simplified due to toxicity associated with any of the constituent components of FOLFIRINOX/NALIRIFOX (e.g. simplified to FOLFOX, FOLFIRI, 5-FU (including capecitabine)) will be eligible.

- Patients with progressive disease while on maintenance PARP inhibitor treatment after FOLFIRINOX (or NALIRIFOX), irrespective of how long ago they received FOLFIRINOX/NALIRIFOX, will also be eligible.
- Patients who develop metastatic disease during or within 6 months after completing FOLFIRINOX/NALIRIFOX in either the locally advanced or adjuvant/neoadjuvant settings will be eligible.

___ **3.2.6 Patients may not have received prior cisplatin for their pancreatic cancer in any setting.**

Note: Patients may have previously received gemcitabine +/- nab-paclitaxel for resectable (neoadjuvant/adjuvant) or locally advanced disease if (1) treatment was completed > 1 year ago and (2) in the opinion of the treating provider, re-treatment with gemcitabine/nab-paclitaxel is appropriate.

___ **3.2.7 Age ≥ 18 years**

___ **3.2.8 ECOG Performance Status 0-2 (Karnofsky Performance Status ≥60).**

___ **3.2.9 Required Initial Laboratory Values**

• Absolute Neutrophil Count	≥1,500/mm^3
• Platelet Count	≥ 100,000/mm^3
• Hemoglobin	≥ 8.0 g/dL
• Creatinine	≤ 1.8 x institutional upper limit of normal (ULN)
OR	
Calc. CrCl	> 40 mL/min
• Total Bilirubin	≤ 2.0 x institutional ULN*
• AST/ALT	≤ 3 x institutional ULN **

* Any elevated bilirubin should be asymptomatic at enrollment) except for participants with documented Gilbert's syndrome who may only be included if the total bilirubin ≤ 3 x ULN or direct bilirubin ≤ 1.5 x ULN).

** AST/ALT of ≤ 5 x ULN if liver metastases are present.

___ **3.2.10 Not pregnant and not nursing,** because this study involves an agent that has known genotoxic, mutagenic and teratogenic effects.

Therefore, for women of childbearing potential only, a negative pregnancy test done ≤ 14 days prior to registration is required.

___ **3.2.11** Patients with > grade 2 peripheral sensory neuropathy are not eligible.

___ **3.2.12** Patients with a prior or concurrent malignancy whose natural history or treatment does not have the potential to interfere with the safety or efficacy assessment of the investigational regimen are eligible for this trial.

___ **3.2.13 Brain metastases:** Patients with **treated brain metastases** are eligible if follow-up brain imaging after CNS-directed therapy shows no evidence of progression for at least 8-weeks.

Patients with known, new or progressive brain metastases (active brain metastases) or leptomeningeal disease are ineligible.

___ **3.2.14 HIV:** HIV-infected patients on effective anti-retroviral therapy with undetectable viral load anytime within 6 months prior to registration are eligible for this trial.

___ **3.2.15 Hepatitis B:** For patients with evidence of chronic hepatitis B virus (HBV) infection, the HBV viral load must be undetectable on suppressive therapy, if indicated.

Hepatitis C: Patients with a history of hepatitis C virus (HCV) infection must have been treated and cured. For patients with HCV infection who are currently on treatment, they are eligible if they have an undetectable HCV viral load.

___ **3.2.16 Concomitant medications**

Concomitant Chronic concomitant treatment with strong inhibitors of CYP3A4 is not allowed on this study. Patients on strong CYP3A4 inhibitors must discontinue the drug for 14 days prior to registration on the study. See section 8.1.9 for more information.

Chronic concomitant treatment with strong CYP3A4 inducers is not allowed. Patients must discontinue the drug 14 days prior to the start of study treatment. See section 8.1.10 for more information.

4.0 PATIENT REGISTRATION

4.1 Investigator and Research Associate registration with CTEP

Food and Drug Administration (FDA) regulations require sponsors to select qualified investigators. National Cancer Institute (NCI) policy requires all individuals contributing to NCI-sponsored trials to register with their qualifications and credentials and to renew their registration annually. To register, all individuals must obtain a Cancer Therapy Evaluation Program (CTEP) Identity and Access Management (IAM) account at https://ctepcore.nci.nih.gov/iam. Investigators and clinical site staff who are significant contributors to research must register in the Registration and Credential Repository (RCR). The RCR is a self-service online person registration application with electronic signature and document submission capability.

RCR utilizes five person registration types.

- **Investigator (IVR)**—MD, DO, or international equivalent;
- **Non-Physician Investigator (NPIVR)**—advanced practice providers (e.g., NP or PA) or graduate level researchers (e.g., PhD);
- **Associate Plus (AP)**—clinical site staff (e.g., RN or CRA) with data entry access to CTSU applications such as the Roster Update Management System (RUMS), OPEN, Rave; acting as a primary site contact, or with consenting privileges
- **Associate (A)—**other clinical site staff involved in the conduct of NCI-sponsored trials; and
- **Associate Basic (AB)**—individuals (e.g., pharmaceutical company employees) with limited access to NCI-supported systems.

RCR requires the following registration documents:

Documentation Required	IVR	NPIVR	AP	A	AB
FDA Form 1572	✓	✓			
Financial Disclosure Form	✓	✓	✓		
NCI Biosketch (education, training, employment, license, and certification)	✓	✓	✓		
GCP training	✓	✓	✓		
Agent Shipment Form (if applicable)	✓				
CV (optional)	✓	✓	✓		

IVRs and NPIVRs must list all clinical practice sites and Institutional Review Boards (IRBs) covering their practice sites on the FDA Form 1572 in RCR to allow the following::

- Addition to a site roster;
- Selection as the treating, credit, or drug shipment investigator or consenting person in OPEN;
- Ability to be named as the site-protocol Principal Investigator (PI) on the IRB approval; and
- Assignment of the Clinical Investigator (CI) task on the Delegation of Tasks Log (DTL).

In addition, all investigators acting as the Site-Protocol PI (investigator listed on the IRB approval), consenting/treating/drug shipment investigator in OPEN, or as the CI on the DTL must be rostered at the enrolling site with a participating organization.

Refer to the NCI RCR page on the CTEP website for additional information. For questions, please contact the **RCR Help Desk** by email at RCRHelpDesk@nih.gov.

4.2 Cancer Trials Support Unit registration procedures

Permission to view and download this protocol and its supporting documents is restricted and is based on the person and site roster assignment housed in the Roster Maintenance application and in most cases viewable and manageable via the Roster Update Management System (RUMS) on the Cancer Trials Support Unit (CTSU) members' website. See Section 4.2.2.

This study is supported by the NCI CTSU.

IRB Approval:

As of March 1, 2019, all U.S.-based sites must be members of the NCI Central Institutional Review Board (NCI CIRB) in order to participate in Cancer Therapy Evaluation Program (CTEP) and Division of Cancer Prevention (DCP) studies open to the National Clinical Trials Network (NCTN) and NCI Community Oncology Research Program (NCORP) Research Bases. In addition, U.S.-based sites must accept the NCI CIRB review to activate new studies at the site after March 1, 2019. Local IRB review will continue to be accepted for studies that are not reviewed by the CIRB, or if the study was previously open at the site under the local IRB. International sites should continue to submit Research Ethics Board (REB) approval to the CTSU Regulatory Office following country-specific regulations.

Sites participating with the NCI CIRB must submit the Study Specific Worksheet (SSW) for Local Context to the CIRB using IRBManager to indicate their intent to open the study locally. The NCI CIRB's approval of the SSW is automatically communicated to the CTSU Regulatory

Office, but sites are required to contact the CTSU Regulatory Office at CTSURegPref@ctsu.coccg.org to establish site preferences for applying NCI CIRB approvals across their Signatory Network. Site preferences can be set at the network or protocol level. Questions about establishing site preferences can be addressed to the CTSU Regulatory Office by email or calling 1-888-651-CTSU (2878).

In addition, the Site-Protocol Principal Investigator (PI) (i.e., the investigator on the IRB/REB approval) must meet the following criteria for the site to be able to have an Approved status following processing of the IRB/REB approval record:

- Have an Active CTEP status;
- Have an active status at the site(s) on the IRB/REB approval on at least one participating organization's roster;
- If using NCI CIRB, be active on the NCI CIRB roster under the applicable CIRB Signatory Institution(s) record;
- Include the IRB number of the IRB providing approval in the Form FDA 1572 in the RCR profile;
- List all sites on the IRB/REB approval as Practice Sites in the Form FDA 1572 in the RCR profile; and
- Have the appropriate CTEP registration type for the protocol.

4.2.1 Additional site registration requirements

Additional site requirements to obtain an approved site registration status include:

- An active Federal Wide Assurance (FWA) number;
- An active roster affiliation with the Lead Protocol Organization (LPO) or a Participating Organization (PO);
- An active roster affiliation with the NCI CIRB roster under at least one CIRB Signatory Institution (U.S. sites only); and
- Compliance with all applicable protocol-specific requirements (PSRs).

4.2.2 Downloading Site Registration Documents

Download the site registration forms from the protocol-specific page located on the CTSU members' website. Permission to view and download this protocol and its supporting documents is restricted to institutions and their associated investigators and staff on a participating roster. To view/download site registration forms:

- Log in to the CTSU members' website (https://www.ctsu.org);
- Click on *Protocols* in the upper left of the screen:
  - Enter the protocol number in the search field at the top of the protocol tree, or
  - Click on the By Lead Organization folder to expand, then select *Alliance*, and protocol number A022106.
- Click on *Documents*, *Protocol Related Documents*, and use the *Document Type* filter and select *Site Registration* to download and complete the forms provided. (Note: For sites under the CIRB, IRB data will load automatically to the CTSU.)

4.2.3 Submitting regulatory documents

Submit required forms and documents to the CTSU Regulatory Office using the Regulatory Submission Portal on the CTSU members' website.

To access the Regulatory Submission Portal log in to the CTSU members' website, go to the Regulatory section and select Regulatory Submission.

Institutions with patients waiting that are unable to use the Regulatory Submission Portal should alert the CTSU Regulatory Office immediately by phone or email: 1-866-651-CTSU (2878), or CTSURegHelp@coccg.org to receive further instruction and support.

4.2.4 Checking site registration status

Site registration status may be verified on the CTSU members' website.

- Click on *Regulatory* at the top of the screen;
- Click on *Site Registration*; and
- Enter the site's 5-character CTEP Institution Code and click on Go:
  - Additional filters are available to sort by Protocol, Registration Status, Protocol Status, and/or IRB Type.

Note: The status shown only reflects institutional compliance with site registration requirements as outlined within the protocol. It does not reflect compliance with protocol requirements for individuals participating on the protocol or the enrolling investigator's status with NCI or their affiliated networks.

4.3 Patient Registration Requirements

4.3.1 Informed consent

The patient must be aware of the neoplastic nature of his/her disease and willingly consent after being informed of the procedure to be followed, the experimental nature of the therapy, alternatives, potential benefits, side-effects, risks, and discomforts. Current human protection committee approval of this protocol and a consent form is required prior to patient consent and registration.

Patients with impaired decision making capacity may be enrolled on this study, where institutional policy and IRB of record allow.

4.4 Patient Registration/randomization procedures

The Oncology Patient Enrollment Network (OPEN) is a web-based registration system available on a 24/7 basis. OPEN is integrated with CTSU regulatory and roster data and with the LPOs registration/randomization systems or the Theradex Interactive Web Response System (IWRS) for retrieval of patient registration/randomization assignment. OPEN will populate the patient enrollment data in NCI's clinical data management system, Medidata Rave.

Requirements for OPEN access:

- A valid CTEP-IAM account;
- To perform enrollments or request slot reservations: Must be on an LPO roster, ETCTN Corresponding roster, or participating organization roster with the role of Registrar. Registrars must hold a minimum of an Associate Plus (AP) registration type;
- If a Delegation of Tasks Log (DTL) is required for the study, the registrars must hold the OPEN Registrar task on the DTL for the site; and
- Have an approved site registration for the protocol prior to patient enrollment.

To assign an Investigator (IVR) or Non-Physician Investigator (NPIVR) as the treating, crediting, consenting, drug shipment (IVR only), or receiving investigator for a patient transfer in OPEN, the IVR or NPIVR must list the IRB number used on the site's IRB approval on their

Form FDA 1572 in RCR. If a DTL is required for the study, the IVR or NPIVR must be assigned the appropriate OPEN-related tasks on the DTL.

Prior to accessing OPEN, site staff should verify the following:

- Patient has met all eligibility criteria within the protocol stated timeframes; and
- All patients have signed an appropriate consent form and HIPAA authorization form (if applicable).

Note: The OPEN system will provide the site with a printable confirmation of registration and treatment information. You may print this confirmation for your records.

Access OPEN at https://open.ctsu.org or from the OPEN link on the CTSU members' website. Further instructional information is in the OPEN section of the CTSU website at https://www.ctsu.org or https://open.ctsu.org. For any additional questions, contact the CTSU Help Desk at 1-888-823-5923 or ctsucontact@westat.com.

4.5 Stratification Factors and Treatment Assignments

The randomization routine is found in Section 13.0 (Statistical Considerations).

4.5.1 Stratification Factors

1) Best response to first-line treatment (SD/PR/CR vs. PD/non-evaluable).

   Best response to prior treatment will be assessed by the treating provider and confirmed by the study P.I.s (Drs. Ko and Tsang) prior to randomization, based on review of available imaging reports. Formal RECIST reads during first-line treatment are NOT required for eligibility/stratification purposes. Patients whose first-line treatment was discontinued due to toxicity before formal response assessment could be performed will be classified as non-evaluable.

2) Platinum resistant (defined as disease progression on or within 12 weeks of last platinum dose) vs platinum sensitive (no progression on platinum).

4.5.2 Treatment Assignments

The factors defined in Section 4.6.1 will be used as stratification factors.

After the patient has been registered into the study, the values of the stratification factors will be recorded, and the patient will be assigned to one of the following treatment groups using the Pocock and Simon dynamic allocation procedure which balances the marginal distributions of the stratification factors between the treatment groups.

1) Arm 1: Gemcitabine, nab-paclitaxel, and cisplatin (days 1 and 15 of 28 day cycles).
2) Arm 2: Gemcitabine and nab-paclitaxel (days 1 and 15 of 28 day cycles).

5.0 STUDY CALENDAR

Laboratory and clinical parameters during treatment are to be followed using individual institutional guidelines and the best clinical judgment of the responsible physician. It is expected that patients on this study will be cared for by oncology providers experienced in the treatment and supportive care of patients on this trial.

Pre-study Testing Intervals

The pre-study testing intervals are guidelines only. However, testing done beyond these intervals may be considered deviations. When calculating days of tests and measurements, the day a test or measurement is done is considered Day 0. Therefore, if a test were done on a Monday, the Monday one week later would be considered Day 7.

To be completed ≤ 30 DAYS before registration: All laboratory studies, history and physical.

To be completed ≤ 30 DAYS before registration: Any X-ray, scan of any type or ultrasound which is utilized for tumor measurement per protocol.

	Prior to Registration (Step 1)* (Screening)	**Day 1 of Each Cycle***	**Day 15 each Cycle**	**End of Treatment Visit****	**Post-treatment follow up*****
H&P, weight, vitals, PS	X(1)	X(1)		X(1)	
Height	X				
Adverse Event Assessment (CTCAE Assessment)	X	X		X	
CBC, Differential, Platelets	X	X	X	X	
Chemistry (Na, K, Ca, Mg, BUN/Creatinine)	X	X	X	X	
AST, ALT, Alk. Phos., Total Bilirubin, Albumin	X	X	X	X	
BRCA1/2 or PALB2 mutation	X				
Serum or Urine HCG	X(2)				
CA 19-9	X(3)	X(3)		X(3)	
Staging					
CT (chest) or MRI (abd/pelvis)	X(4)	A(4)		A(4)	A(4)
Correlative studies: For all patients consented to biobanking					
Blood Samples (A022106 Biobanking)	*See Section 6.2*				
Archival Tumor Tissue	*See section 6.2*				

*	Labs completed prior to registration may be used for day 1 of cycle 1 tests if obtained ≤ 7 days prior to treatment. For subsequent cycles, labs, scans, tests and observations may be obtained ≤ 72 hours prior to day of treatment. Patients can be pre-registered while on front-line FOLFIRINOX and/or maintenance PARP inhibitor.
**	End of treatment visit required within 30 days of the last dose of study treatment.
***	Physical examination and staging scans are required ≤ 4 weeks prior to starting on study, then every 8 weeks until disease progression; thereafter, survival information is required every 3 months until 2 years following end of treatment. See also Section 12.0.
1	Drug dosages need not be changed unless the calculated dose changes by ≥ 10%.
2	For women of childbearing potential (see Section 3.3.9). Must be done ≤ 14 days prior to registration.
3	Any measurements of biochemical response should occur in conjunction with the radiologic assessments for disease status (ideally within 14 days if possible). CA 19-9 will be drawn on day 1 of every other cycle starting C1D1 (e.g. C1D1, C3D1, etc.). More frequent CA19-9 measurements (for example, at C2D1, C4D1, etc.) may be obtained per institutional/practice standard.
4	Scans can include either: 1) a CT or MRI performed with IV (+/-PO) contrast. The same imaging modality used at baseline should be used for all subsequent evaluations. CT scans are preferred and should be of diagnostic quality and performed with IV contrast unless there is a medical contraindication. MRI scans should be of diagnostic quality and performed with IV contrast unless there is a medical contraindication. MRI is the preferred imaging modality for patients with a medical contraindication to CT contrast. Imaging completed within 30 days prior to registration can be used as baseline imaging. Supporting documentation is to be submitted per Section 6.1.4.
A	Every 8 weeks (+/- 1 week) from Cycle 1 Day 1 until evidence of disease progression. The same imaging modality used at baseline should be used for all subsequent evaluations. Supporting documentation is to be submitted per Section 6.1.1.

6.0 DATA AND SPECIMEN SUBMISSION

6.1 Data Collection and Submission

6.1.1 Data submission schedule

A Data Submission Schedule (DSS) is available on the Alliance study webpage, within the Case Report Forms section. The Data Submission Schedule is also available on the CTSU site within the study-specific Case Report Forms folder.

6.1.2 Medidata Rave

Medidata Rave is the clinical data management system being used for data collection for this trial/study. Access to the trial in Rave is controlled through the CTEP-IAM system and role assignments.

Requirements to access Rave via iMedidata:

- Active CTEP registration with the credentials necessary to access secure NCI/CTSU IT systems; and
- Assigned a Rave role on the LPO or PO roster at the enrolling site of: Rave CRA, Rave Read Only, Rave CRA (LabAdmin), Rave SLA, or Rave Investigator.

Rave role requirements:

- Rave CRA or Rave CRA (Lab Admin) role must have a minimum of an Associate Plus (AP) registration type;
- Rave Investigator role must be registered as a Non-Physician Investigator (NPIVR) or Investigator (IVR); and
- Rave Read Only or Rave SLA role must have at a minimum an Associates (A) registration type.

Refer to https://ctep.cancer.gov/investigatorResources/default.htmfor registration types and documentation required.

Upon initial site registration approval for the study in the Regulatory application, all persons with Rave roles assigned on the appropriate roster will be sent a study invitation email from iMedidata. To accept the invitation, site staff must either click on the link in the email or log in to iMedidata via the CTSU members' website under *Data Management > Rave Home* and click to *accept* the invitation in the *Tasks* pane located in the upper right corner of the iMedidata screen. Site staff will not be able to access the study in Rave until all required Medidata and study-specific trainings are completed. Trainings will be in the form of electronic learnings (eLearnings) and can be accessed by clicking on the eLearning link in the *Tasks* pane located in the upper right corner of the iMedidata screen. If an eLearning is required for a study and has not yet been taken, the link to the eLearning will appear under the study name in the *Studies* pane located in the center of the iMedidata screen; once the successful completion of the eLearning has been recorded, access to the study in Rave will be granted, and a *Rave EDC* link will replace the eLearning link under the study name.

Site staff who have not previously activated their iMedidata/Rave account at the time of initial site registration approval for the study in the Regulatory application will receive a separate invitation from iMedidata to activate their account. Account activation instructions are located on the CTSU website in the *Data Management* section under the Rave resource materials (*Medidata Account Activation and Study Invitation Acceptance*).

Additional information on iMedidata/Rave is available on the CTSU members' website in the *Data Management > Rave* section or by contacting the CTSU Help Desk at 1-888-823-5923 or by email at ctsucontact@westat.com.

6.1.3 Data Quality Portal

The Data Quality Portal (DQP) provides a central location for site staff to manage unanswered queries and form delinquencies, monitor data quality and timeliness, generate reports, and review metrics.

The DQP is located on the CTSU members' website under Data Management. The Rave Home section displays a table providing summary counts of Total Delinquencies and Total Queries. DQP Queries, DQP Delinquent Forms, DQP Form Status, and the DQP Reports modules are available to access details and reports of unanswered queries, delinquent forms, forms with current status and timeliness reports. Site staff should review the DQP modules on a regular basis to manage specified queries and delinquent forms.

The DQP is accessible by site staff who are rostered to a site and have access to the CTSU website. Staff who have Rave study access can access the Rave study data via direct links available in the DQP modules.

CTSU Delinquency Notification emails are sent to primary contacts at sites twice a month. These notifications serve as alerts that queries and/or delinquent forms require site review, providing a summary count of queries and delinquent forms for each Rave study that a site is participating in. Additional site staff can subscribe and unsubscribe to these notifications using the CTSU Report and Information Subscription Portal on the CTSU members' website.

To learn more about DQP use and access, click on the Help Topics icon displayed on the Rave Home, DQP Queries, DQP Delinquent Forms, DQP Form Status, and DQP Reports modules.

This study does not use the Rave Calendaring functionality and therefore the DQP Delinquent Forms module will not include details for this study, and the DQP Summary table on the Rave Home page will display *N/A* for the Total Delinquencies summary count.

6.1.4 Supporting documentation to be submitted to the Alliance

This study requires supporting documentation for diagnosis, response, progression, other. Supporting documentation will include local pathology reports, clinic notes, imaging reports, and other documents/notes/reports, and these must be submitted at the following time points:

- **Baseline:** Clinic notes, imaging report, pathology/cytology, BRCA1/2 or PALB2 mutation report; Documentation of previous first-line FOLFIRINOX or NALIRIFOX +/- maintenance PARP inhibitor treatment, including documentation of disease progression on first-line treatment and best response to first-line treated)
- **Treatment:** Clinic notes, including CA 19-9, imaging reports.
- **Progression:** Clinic notes, including CA 19-9, imaging report, pathology reports (if applicable), including repeat somatic profiling.

Supporting documentation is to be submitted via Rave.

6.2 Specimen Collection and Submission

The Alliance A022106 Correlative Science Manual (CSM) contains instructions for specimen collection, processing and shipping. The manual can be found on the BioMS and CTSU

websites. Questions regarding the CSM should be addressed to the contacts specified in the manual.

For patients consenting to biobanking: All participating institutions must ask patients for their consent to participate in biobanking for future research, although patient participation is optional. Biomarker studies will be performed. Rationale and methods for the scientific components of these studies are described in Section 14.2. For patients who consent to participate, blood and tissue will be collected at the time points listed below for these studies:

Time points	Baseline (C1D1; prior to treatment)	C2D1	Progression
For all patients consented to biobanking			
Archival Tumor Tissue	x		
Plasma from EDTA whole blood	1x10ml	1x10ml	1x10ml
Whole blood in Streck tubes for ctDNA	3x10ml	3x10ml	3x10ml

7.0 TREATMENT PLAN/INTERVENTION

Protocol treatment is to begin ≤ 14 days of registration.

For questions regarding treatment, please see the study contacts page.

Patients must have completed prior therapy (FOLFIRINOX or NALIRIFOX or any of the associated components of these regimens, if subsequently simplified; as well as PARP inhibition if patient was on maintenance treatment) within 6 months prior to the start of protocol treatment.

It is acceptable for individual chemotherapy doses to be delivered ≤ a 48-hour (2 business day) window before and after the protocol-defined date for Day 1 of a new cycle. For example, if the treatment due date is a Friday, the window for treatment includes the preceding Thursday through the following Monday. In addition, patients are permitted to have a new cycle of chemotherapy delayed up to 7 days for major life events (e.g., serious illness in a family member, major holiday, vacation that cannot be rescheduled) without this being considered a protocol violation. Documentation to justify this delay should be provided.

Patients will be randomized to either Arm 1 or Arm 2. Protocol therapy will consist of treatment on either arm 1 or arm 2 administered on days 1 and 15 of a 28-day cycle. Treatment will continue until disease progression or unacceptable adverse event. No maximum duration of therapy is specified.

7.1 Arm 1: Nab-paclitaxel plus cisplatin plus gemcitabine

Agent	Dose	Route	Day	Cycle
Nab-paclitaxel	100 mg/m^2	IV over 30-40 mins (+/- 5 mins)	Days 1 and 15	Every 28 days
gemcitabine	800 mg/m^2	IV over 30-40 mins (+/- 5 mins)	Days 1 and 15	Every 28 days
cisplatin	25 mg/m^2	IV over 30-60 mins (+/- 5 mins)	Days 1 and 15	Every 28 days

* Order of infusion: nab-paclitaxel, cisplatin, then gemcitabine

7.2 Arm 2: Nab-paclitaxel plus gemcitabine

Agent	Dose	Route	Day	Cycle
Nab-paclitaxel	125 mg/m^2	IV over 30-40mins (+/- 5 mins)	Days 1 and 15	Every 28 days
gemcitabine	1000 mg/m^2	IV over 30-40 mins (+/- 5 mins)	Days 1 and 15	Every 28 days

* Nab-paclitaxel given prior to gemcitabine

8.0 DOSE AND TREATMENT MODIFICATIONS

8.1 Ancillary Therapy, Concomitant Medications, and Supportive Care

8.1.1 Patients should not receive any other treatment which would be considered treatment for the primary neoplasm or impact the primary endpoint. This includes any surgical intervention, radiotherapy, cryotherapy, ablation, etc., performed on the primary neoplasm.

8.1.2 **Patients should receive full supportive care while on this study.** This includes blood product support, antibiotic treatment, and treatment of other newly diagnosed or concurrent medical conditions. All blood products and concomitant medications such as antidiarrheals, analgesics, and/or antiemetics received from the first day of study treatment administration until 30 days after the final dose will be recorded in the medical records.

8.1.3 **Treatment with hormones or other chemotherapeutic agents may not be administered** except for steroids given for adrenal failure; hormones administered for

non-disease-related conditions (e.g., insulin for diabetes); and intermittent use of dexamethasone as an antiemetic.

8.1.4 Antiemetics may be used at the discretion of the attending physician.

Subjects on study should receive prophylactic antiemetics per institutional standards, which may include prochlorperazine, a 5HT-3 antagonist, steroid, and/or NK1 antagonist.

Additionally, patients receiving cisplatin (arm 1) should receive adequate pre- and/or post-hydration per institutional standards.

8.1.5 Diarrhea management is per the discretion of the treating physician. Diarrhea could be managed conservatively with medications such as loperamide.

Patients with severe diarrhea should be assessed for intravenous hydration and correction of electrolyte imbalances.

8.1.6 Palliative radiation therapy may not be administered while a patient is on study. Irradiate a symptomatic lesion, or one that may produce disability (e.g., unstable femur) prior to study initiation, provided other measurable disease is present.

Patients who require radiation therapy during protocol treatment will be removed from protocol therapy due to disease progression.

8.1.7 Alliance Policy Concerning the Use of Growth Factors

Blood products and growth factors should be utilized as clinically warranted and following institutional policies and recommendations. The use of growth factors should follow published guidelines of the American Society of Clinical Oncology Clinical Practice Guideline Update. J Clin Oncol 33: 3199-3212, 2015 and American Society of Clinical Oncology – American Society of Hematology Clinical Practice Guideline Update on the Use of Epoetin and Darbepoetin in Adult Patients with Cancer. J Clin Oncol 28:4996-5010, 2010.

The use of prophylactic white blood cell (WBC) growth factor support is permitted but not mandated for all trial participants during chemotherapy starting with the first treatment cycle. Local institutional policies should be followed where use of WBC growth factor support is restricted and/or prohibited; see Section 7.1. If used, these are to be obtained from commercial sources. In circumstances where a patient's neutrophil count is markedly elevated per institutional standard at the start of a new treatment cycle, growth factor may be omitted for that cycle per treating physician discretion and clinically recommended guidelines.

Blood products should be utilized as clinically warranted and following institutional policies and recommendations.

Use of epoetin (EPO), filgrastim (G-CSF), tbo-filgrastim, pegfilgrastim, sargramostim (GM-CSF), and/or WBC biosimilar products are permitted at the discretion of the treating physician per clinically recommended guidelines. Filgrastim/pegfilgrastim are preferred.

White blood cell growth factor may be used per institutional guidelines.

8.1.8 Hypersensitivity/infusion reactions

Treat hypersensitivity and infusion reactions to each chemotherapy agent per institutional standards.

8.1.9 CYP3A4 Inhibitors

Chronic concomitant treatment with strong inhibitors of CYP3A4 is not allowed during on this trial. The following drugs are EXAMPLES of strong inhibitors of CYP3A4 and are not allowed during treatment with nab-paclitaxel.

- Indinavir
- Clarithromycin
- Ketoconazole

Because lists of these agents are constantly changing, please consult and review any drugs for their potential to inhibit CYP3A4. Examples of resources that may be utilized include the product information for the individual concomitant drug in question, medical reference texts such as the Physicians' Desk Reference, the FDA website, or your local institution's pharmacist.

8.1.10 CYP3A4 Inducers

Chronic concomitant treatment with strong inducers of CYP3A4 is not allowed during on this trial. The following drugs are EXAMPLES of strong inducers of CYP3A4 and are not allowed during treatment with nab-paclitaxel.

- Rifampin
- Carbamazepine

Because lists of these agents are constantly changing, please consult and review any drugs for their potential to induce CYP3A4. Examples of resources that may be utilized include the product information for the individual concomitant drug in question, medical reference texts such as the Physicians' Desk Reference, the FDA website, or your local institution's pharmacist.

8.2 Dose Modifications

8.2.1 General considerations

If multiple adverse events are seen, administer dose based on greatest reduction required for any single adverse event observed. Reductions apply to treatment given in the preceding cycle and are based on adverse events observed since the prior dose. Dose modifications of each individual chemotherapy agent may occur independently of one another based on the pattern of toxicity. Dosing is based on actual body weight.

All chemotherapeutic agents will not be re-escalated once reduced.

No dose reductions below DL-2 are permitted. One or two drugs may be held for toxicity.

The maximum dose delay (from the time of a scheduled treatment) for any reason is 4 weeks.

Patients on either arm may continue protocol treatment as long as all drugs do not need to be discontinued for toxicities. Specifically, patients may continue on protocol treatment as long as at least one of the study drugs continues despite other agent(s) being held for toxicity.

AERS reporting may be required for some adverse events (See Section 9.0).

8.2.2 Dose Levels

For Arm 1: gemcitabine, nab-paclitaxel, and cisplatin

Drug Name	Initial dose	Dose level -1	Dose level -2
Gemcitabine	800 mg/m2	600 mg/m2	500 mg/m2
Nab-paclitaxel	100 mg/m2	75 mg/m2	50 mg/m2
Cisplatin	25 mg/m2	20 mg/m2	15 mg/m2

For Arm 2: gemcitabine and nab-paclitaxel

Drug Name	Initial dose	Dose level -1	Dose level -2
Gemcitabine	1000 mg/m2	800 mg/m2	600 mg/m2
Nab-paclitaxel	125 mg/m2	100 mg/m2	75 mg/m2

8.2.3 Hematologic Toxicities

The following guidelines apply to both day 1 and day 15 of each treatment cycle. Please note that the Table of Dose Modifications for Hematologic Toxicity (below) represent suggested guidelines; the treating provider may use their own institutional practice and clinical judgment to decide on the need for dose modifying.

- If treatment is delayed on day 1 of a cycle, then that new cycle would begin upon count recovery (which would then represent the new day 1 of that cycle).
- If treatment is delayed on day 15 of a cycle, then:
    - If blood counts recover within one week, the treatment administered would be considered part of that same cycle (e.g. cycle X day 22), and the subsequent cycle would be scheduled to begin 2 weeks after that.
    - If blood counts do not recover within one week, then that day 15 dose would be skipped, and resumption of treatment would represent the start of a new cycle.

Dose Modifications for Day 1 or Day 15 (Hematologic Toxicity)

Laboratory results	Treat	Gemcitabine (both arms)	Nab-paclitaxel (both arms)	Cisplatin (arm 1 only)
ANC > 1,000 and plts > 75K	On time	No modification	No modification	No modification
ANC 500-1,000 or plts 50-75K	Delay treatment by 1 week intervals until recovery	First occurrence: No modification, consider adding growth factor support	First occurrence: No modification, consider adding growth factor support	No modification

		Second or beyond occurrence: Decrease by 1 level and consider adding growth factor support	Second or beyond occurrence: Decrease by 1 level and consider adding growth factor support	
ANC<500 or plts <50K	Delay treatment by 1 week intervals until recovery	Decrease by 1 level and consider adding growth factor support	Decrease by 1 level and consider adding growth factor support	No modification
Febrile neutropenia (grade 3 or 4)	Delay treatment by 1 week intervals until recovery (inc afebrile x at least 48 hrs)	Decrease by 1 level and consider adding growth factor support	Decrease by 1 level and consider adding growth factor support	Decrease by 1 level and consider adding growth factor support

Note: No dose modification will be required for anemia as it can be satisfactorily managed by transfusions.

8.2.4 Non-Hematologic Toxicities

All treatment related non-hematological toxicities (with the exception of hair loss and nausea and vomiting that can be controlled with antiemetics) should resolve to ≤ Grade 2 prior to every dose.

Alopecia and nausea and/or vomiting that can be controlled by antiemetics do not require dose modification.

Dose modification or delay may occur in the setting of lower grade toxicity if the treating physician believes that it is in the interest of a subject's safety.

CTCAE Grade	Treatment Modification
Grade 0-2 toxicity	Same as Day 1 previous cycle (except for Grade 2 cutaneous toxicity where doses of nab-paclitaxel and gemcitabine should be reduced to next lower dose level – see below)
Grade 3 toxicity	Hold all drugs until resolution to ≤ Grade 1. Then resume treatment at the next lower dose level for all drugs[a]. Please see below for specific guidance for select toxicities, including neuropathy and pneumonitis.
Grade 4 toxicity	Hold all drugs until resolution to ≤ Grade 1. Then resume treatment at the next lower dose level for all drugs. Please see below for specific guidance for select toxicities, including neuropathy and pneumonitis.

Notes:

- Dose modifications for specific toxicities (peripheral sensorimotor neuropathy, nephrotoxicity) are noted in sections below.
- If a specific toxicity can be clearly attributed to only one drug (i.e. cisplatin-associated hypomagnesemia or ototoxicity; nab-paclitaxel-associated myalgias), it is permissible to hold only that drug and continue with the others. When toxicity resolves to ≤grade 1, then resume treatment at the next lower dose level of only that specific drug. For cisplatin induced ototoxicity, patient should undergo an audiology consult and cisplatin either held or discontinued per audiology recommendations.

- In the setting of hyperbilirubinemia secondary to obstruction that can be addressed with a stent, dose reduction is not required and will be left to the discretion of the treating physician. Treatment can be delayed until resolution of hyperbilirubinemia, as per institutional guidelines,
- Grade 3 nausea, vomiting, and/or diarrhea that can controlled with optimal medical management within 5 days, or grade 3 fatigue that resolves within 5 days, will be exempt from the above dose reduction requirements.
- Pulmonary embolism (a CTCAE Grade 4 toxicity) if mild or asymptomatic will be exempt from the above dose reduction requirements.
- Clinically insignificant electrolyte abnormalities per judgment of the physician/investigator will be exempt from the above dose reduction requirements.

8.2.5 Peripheral Sensorimotor Neuropathy (PSN)

Refer to table below. Gemcitabine can be administered on time without any dose reduction.

<table>
<tr><th>PSN</th><th colspan="2">Arm 1</th><th>Arm 2</th></tr>
<tr><td></td><td>Nab-paclitaxel</td><td>Cisplatin</td><td>Nab-paclitaxel</td></tr>
<tr><td rowspan="2">Grade 2 PSN that persists through the entire cycle (to the time of the next scheduled dose of treatment)</td><td>First episode: Decrease to next lowest dose level

Second episode: No modification</td><td>First episode: No modification

Second episode: Decrease to next lowest dose level</td><td>First episode: Decrease to next lowest dose level</td></tr>
<tr><td colspan="3">If peripheral sensory neuropathy stays at grade 2 after the above dose reductions, dosing can either continue at the same dose levels or be reduced further by one dose level (preferentially reducing nab-paclitaxel before cisplatin) at the discretion of the treating provider.</td></tr>
<tr><td>Grade 3 PSN</td><td>First episode: Hold until grade ≤2, then restart at 1 dose level lower.

Second episode: Hold until grade ≤2, then restart at 1 dose level lower.

Third episode: Permanently discontinue nab-paclitaxel.</td><td>First episode: Hold until grade ≤2, then restart at same dose level.

Second episode: Hold until grade ≤2, then restart at 1 dose level lower.

Third episode: Hold until grade ≤2, then restart at 1 dose level lower.

Fourth episode: Permanently discontinue cisplatin.</td><td>First and second episodes: Hold until grade ≤2, then restart at 1 dose level lower.

Third episode: Permanently discontinue nab-paclitaxel.</td></tr>
<tr><td>Grade 4 PSN</td><td>First episode: Hold until grade ≤2, then</td><td>First episode: Hold until grade ≤2, then restart at 1 dose level lower.</td><td>First episode: Hold until grade ≤2, then restart</td></tr>
</table>

	restart at 2 dose levels lower. Second episode: Permanently discontinue nab-paclitaxel	Second episode: Hold until grade ≤2, then restart cisplatin at same dose level or 1 dose level lower at the discretion of the treating provider. Third episode: Permanently discontinue cisplatin.	at 2 dose levels lower. Second episode: Permanently discontinue nab-paclitaxel.

8.2.6 Nephrotoxicity

Cisplatin (cisplatin injection) produces cumulative nephrotoxicity. The serum creatinine, BUN, creatinine clearance, and magnesium, sodium, potassium, and calcium levels should be measured prior to initiating therapy, and prior to each subsequent course. Cisplatin should not be given unless adequate renal function is confirmed with a calculated creatinine clearance of ≥ 40 mL/min. Gemcitabine and nab-paclitaxel may be administered during this period.

8.2.7 Hypersensitivity and/or Infusion Reactions

Hypersensitivity reactions rarely occur. If they do occur, minor symptoms such as flushing, skin reactions, dyspnea, lower back pain, hypotension, or tachycardia may require temporary interruption of the infusion. However, severe reactions, such as hypotension requiring treatment, dyspnea requiring bronchodilators, angioedema or generalized urticaria require immediate discontinuation of study drug administration and aggressive symptomatic therapy. Patients who experience severe hypersensitivity reactions to nab-paclitaxel should not be re-challenged. It is not recommended to administer nab-paclitaxel to patients with prior hypersensitivity to a taxane. If mild to moderate cisplatin hypersensitivity develops (per NCI CTCAE), the patient may be desensitized using the standard desensitization protocol of the institution. In the setting of a severe hypersensitivity reaction, cisplatin should be discontinued.

8.2.8 Interstitial Pneumonitis

During study participation, patients should be carefully monitored for signs and symptoms of pneumonitis (i.e. Episodes of transient or repeated dyspnea with unproductive persistent cough or fever) and, if observed, immediate clinical evaluation and timely institution of appropriate management (emphasizing the need for corticosteroids if an infectious process has been ruled out as well as appropriate ventilation and oxygen support when required). Administration of study drugs will be permanently discontinued upon making a diagnosis of interstitial pneumonitis.

Prevention, Surveillance and Management of Interstitial Pneumonitis

- During study treatment, episodes of transient or repeated dyspnea with unproductive persistent cough or fever should be paid attention to. Radiographic evaluation with chest X-rays and CT scans (normal or high resolution) may be indicated to look for infiltrates, ground-glass opacities or honeycombing patterns. Pulse oximetry and pulmonary function tests can show respiratory and ventilation compromise.
- Infections should be ruled out with routine immunological/

microbiological methods. Transbronchial lung biopsy is not recommended, given its limited value and risk of pneumothorax and hemorrhage, and should be reserved for cases with unclear etiology.

- Study drug administration should be interrupted upon diagnosis of interstitial pneumonitis and patients permanently discontinued from further study drug treatment. After ruling out an infectious etiology, intravenous high-dose corticosteroid therapy and secondary pathogen coverage should be instituted without delay. Patients with an added immunological component may also require immune modulation with azathioprine or cyclophosphamide. Appropriate ventilation and oxygen support should be used when required.

8.2.8 Dose adjustments for obese patients

There is no clearly documented adverse impact of treatment of obese patients when dosing is performed according to actual body weight. Therefore, all dosing is to be determined solely by actual weight without any modification unless explicitly described in the protocol. This will eliminate the risk of calculation error and the possible introduction of variability in dose administration. Failure to use actual body weight in the calculation of drug dosages will be considered a major protocol deviation. Physicians who are uncomfortable with calculating doses based on actual body weight should recognize that doing otherwise would be a protocol violation. Physicians may consult the published guidelines of the American Society of Clinical Oncology Appropriate Chemotherapy Dosing for Obese Adult Patients with Cancer: American Society of Clinical Oncology Clinical Practice Guideline. J Clin Oncol 30(13): 1553-1561, 2012.

9.0 ADVERSE EVENT REPORTING

The prompt reporting of adverse events is the responsibility of each investigator engaged in clinical research, as required by Federal Regulations. Adverse events must be described and graded using the terminology and grading categories defined in the NCI's Common Terminology Criteria for Adverse Events (CTCAE), Version 5.0. The CTCAE is available at ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm. Attribution to protocol treatment for each adverse event must be determined by the investigator and reported on the required forms. Please refer the NCI Guidelines: Adverse Event Reporting Requirements for further details on AE reporting procedures.

9.1 Routine Adverse Event Reporting

Adverse event data collection and reporting, which are required as part of every clinical trial are done to ensure the safety of patients enrolled in the studies as well as those who will enroll in future studies using similar agents. Adverse events are reported in a routine manner at scheduled times according to the study calendar in Section 5.0. For this trial, "Adverse Events" is used for routine AE reporting in Rave.

9.1.1 Solicited adverse events

The following adverse events are considered "expected" and their presence/absence should be solicited, and severity graded, at baseline and for each cycle of treatment.

CTCAE vX.0 Term	CTCAE v5.0 System Organ Class (SOC)
Neutrophil count decreased	Investigations
Platelet count decreased	Investigations
Creatinine increased	Investigations
Peripheral sensory neuropathy	Nervous system disorders
Fatigue	General disorders
Nausea	Gastrointestinal disorders
Vomiting	Gastrointestinal disorders

9.2 CTCAE Routine Reporting Requirements

In addition to the solicited adverse events listed in Section 9.1, the following table outlines the combinations of time points, grades and attributions of AEs that require routine reporting to the Alliance Statistics and Data Center. Questions about routine reporting should be directed to the Data Manager.

Combinations of CTCAE Grade & Attribution Required for Routine AE Data Submission on Case Report Forms (CRFs)

Attribution	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Unrelated			a	a	a
Unlikely			a	a	a
Possible		a	a, b	a, b	a, b
Probable		a	a, b	a, b	a, b
Definite		a	a, b	a, b	a, b

a) **Adverse Events CRF** - Applies to AEs occurring between registration and within 30 days of the patient's last treatment date.

b) **Adverse Events: Late CRF** - Applies to AEs occurring greater than 30 days after the patient's last treatment date, or as part of the Clinical Follow-up Phase or Survival Follow-

9.3 Expedited Adverse Event Reporting (CTEP-AERS)

Investigators are required by Federal Regulations to report serious adverse events as defined in the table below. CTCAE term (AE description) and grade: The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 will be utilized for AE reporting. All appropriate treatment areas should have access to a copy of the CTCAE version 5.0. A copy of the CTCAE version 5.0 can be downloaded from the CTEP web site https://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm

For further information on the NCI requirements for SAE reporting, please refer to the 'NCI Guidelines for Investigators: Adverse Event Reporting Requirements' document published by the NCI.

Use the NCI protocol number and the protocol-specific patient ID provided during trial registration on all reports.

Note: A death on study requires both routine and expedited reporting, regardless of causality as long as the death occurred within 30 days after the last administration of the investigational agent. Attribution to treatment or other cause must be provided.

Death due to progressive disease should be reported as Grade 5 "Disease progression" in the system organ class (SOC) "General disorders and administration site conditions." Evidence that the death was a manifestation of underlying disease (e.g., radiological changes suggesting tumor growth or progression: clinical deterioration associated with a disease process) should be submitted.

In the rare occurrence when Internet connectivity is lost, a 24-hour notification is to be made to CTEP by telephone at 301-897-7497. Once Internet connectivity is restored, the 24-hour notification phoned in must be entered electronically into CTEP-AERS by the original submitter at the site.

9.3.1 Expedited reporting requirements for adverse events that occur within 30 days of the last administration of the agent/intervention

FDA REPORTING REQUIREMENTS FOR SERIOUS ADVERSE EVENTS (21 CFR Part 312)
NOTE: Investigators **MUST** immediately report to the sponsor (NCI) **ANY** Serious Adverse Events, whether or not they are considered related to the investigational agent(s)/intervention (21 CFR 312.64)
An adverse event is considered serious if it results in **ANY** of the following outcomes:

1) Death
2) A life-threatening adverse event
3) An adverse event that results in inpatient hospitalization or prolongation of existing hospitalization for ≥ 24 hours
4) A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
5) A congenital anomaly/birth defect.
6) Important Medical Events (IME) that may not result in death, be life threatening, or require hospitalization may be considered serious when, based upon 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. (FDA, 21 CFR 312.32; ICH E2A and ICH E6).

ALL SERIOUS adverse events that meet the above criteria **MUST** be immediately reported to the NCI via electronic submission within the timeframes detailed in the table below.

Hospitalization	Grade 1 Timeframes	Grade 2 Timeframes	Grade 3 Timeframes	Grade 4 & 5 Timeframes
Resulting in Hospitalization ≥ 24 hrs	10 Calendar Days			24-Hour 5 Calendar Days
Not resulting in Hospitalization ≥ 24 hrs	Not required		10 Calendar Days	

NOTE: Protocol specific exceptions to expedited reporting of serious adverse events are found in the Specific Protocol Exceptions to Expedited Reporting (SPEER) portion of the CAEPR

Expedited AE reporting timelines are defined as:

- "24-Hour; 5 Calendar Days" - The AE must initially be submitted electronically within 24 hours of learning of the AE, followed by a complete expedited report within 5 calendar days of the initial 24-hour report.
- "10 Calendar Days" - A complete expedited report on the AE must be submitted electronically within 10 calendar days of learning of the AE.

[1]Serious adverse events that occur more than 30 days after the last administration of investigational agent/intervention and have an attribution of possible, probable, or definite require reporting as follows:
Expedited 24-hour notification followed by complete report within 5 calendar days for:

- All Grade 4, and Grade 5 AEs

Expedited 10 calendar day reports for:

- Grade 2 adverse events resulting in hospitalization or prolongation of hospitalization
- Grade 3 adverse events

[2]For studies using PET or SPECT IND agents, the AE reporting period is limited to 10 radioactive half-lives, rounded UP to the nearest whole day, after the agent/intervention was last administered. Footnote "1" above applies after this reporting period.

Effective Date: May 5, 2011

9.3.2 Expedited AE reporting timelines defined

- "24 hours; 5 calendar days" – The investigator must initially report the AE via CTEP-AERS ≤ 24 hours of learning of the event followed by a complete CTEP-AERS report ≤ 5 calendar days of the initial 24-hour report.
- "10 calendar days" - A complete CTEP-AERS report on the AE must be submitted ≤ 10 calendar days of the investigator learning of the event.

Any event that results in persistent or significant disabilities/incapacities, congenital anomalies, or birth defects must be reported via CTEP-AERS if the event occurs following treatment with an agent under an IND.

9.3.3 Additional Instructions or Exclusions to CTEP-AERS Expedited Reporting Requirements

All adverse events reported via CTEP-AERS (i.e., serious adverse events) should also be forwarded to your local IRB.

Treatment expected adverse events include those listed in Section 10.0 and in the package insert.

CTEP-AERS reports should be submitted electronically.

Exclusions

≤ grade 4 hematosuppression and hospitalization resulting from such do not require CTEP-AERS, but should be submitted as part of study results.

Grade 1-3 nausea or vomiting and hospitalization resulting from such do not require AERS reporting, but should be reported via routine AE reporting

Grade 3 nausea or vomiting does not require AERS reporting, but should be reported via routine AE reporting.

9.3.4 Pregnancy

Although not an adverse event in and of itself, pregnancy as well as its outcome must be documented via CTEP-AERS. In addition, the *Pregnancy Information Form* included within the NCI Guidelines for Adverse Event Reporting Requirements must be completed and submitted to CTEP. Any pregnancy occurring in a patient or patient's partner from the time of consent to 90 days after the last dose of study drug must be reported and then followed for outcome. Newborn infants should be followed until 30 days old. Please see the "NCI Guidelines for Investigators: Adverse Event Reporting Requirements for DCTD (CTEP and CIP) and DCP INDs and IDEs" (at http://ctep.cancer.gov/protocolDevelopment/adverse_effects.htm) for more details on how to report pregnancy and its outcome to CTEP.

Pregnancy loss and neonatal death

Pregnancy loss is defined in CTCAE as "Death in utero." Any Pregnancy loss should be reported expeditiously, as Grade 4 "Pregnancy loss" under the Pregnancy, puerperium and perinatal conditions SOC. A Pregnancy loss should NOT be reported as a Grade 5 event under the Pregnancy, puerperium and perinatal conditions SOC, as currently CTEP-AERS recognizes this event as a patient death.

A neonatal death should be reported expeditiously as Grade 4, "Death neonatal" under the General disorders and administration SOC.

9.3.5 New Malignancies

All new malignancies must be reported via CTEP-AERS whether or not they are thought to be related to either previous or current treatment. All new malignancies should be reported, i.e. solid tumors (including non-melanoma skin malignancies), hematologic malignancies, myelodysplastic syndrome/acute myelogenous leukemia, and in situ tumors.

Whenever possible, the CTEP-AERS reports for new malignancies should include tumor pathology, history or prior tumors, prior treatment/current treatment including duration, any associated risk factors or evidence regarding how long the new malignancy may have been present, when and how the new malignancy was detected, molecular characterization or cytogenetics of the original tumor (if available) and of any new tumor, and new malignancy treatment and outcome, if available.

Secondary Malignancy

A secondary malignancy is a cancer caused by treatment for a previous malignancy (e.g., treatment with investigational agent/intervention, radiation or chemotherapy). A secondary malignancy is not considered a metastasis of the initial neoplasm.

Alliance requires all secondary malignancies that occur following treatment with an agent under an Alliance IND/IDE be reported via CTEP-AERS. Three options are available to describe the event:

- Leukemia secondary to oncology chemotherapy (e.g., acute myelocytic leukemia [AML])
- Myelodysplastic syndrome (MDS)
- Treatment-related secondary malignancy

Any malignancy possibly related to cancer treatment (including AML/MDS) should also be reported via Rave.

Second Malignancy

A second malignancy is one unrelated to the treatment of a prior malignancy (and is NOT a metastasis from the initial malignancy). Second malignancies require ONLY routine reporting unless otherwise specified.

10.0 DRUG INFORMATION

10.1 General Considerations:

The total administered dose of chemotherapy may be rounded up or down within a range of 10% of the actual calculated dose per institutional practices.

It is not necessary to change the doses of chemotherapy drugs due to changes in weight unless the calculated dose changes by ≥10% if institution allows or follow institutional standard chemotherapy practices.

All study agents are to be administered at the registering institution.

If the Group credited for enrollment is a non-Alliance Group, then other requirements from the credited Group may apply.

10.2 Nab-paclitaxel (Abraxane®, Paclitaxel protein-bound particles) (NSC #736631).

Procurement

Nab-paclitaxel is not provided for the trial and institutional pharmacy shall obtain supplies from normal commercial supply chain or wholesaler.

Consult the package insert for the most current and complete information.

Nab-paclitaxel is a microtubule inhibitor that promotes the assembly of microtubules from tubulin dimers and stabilizes microtubules by preventing depolymerization. This stability results in the inhibition of the normal dynamic reorganization of the microtubule network that is essential for vital interphase and mitotic cellular functions. Paclitaxel induces abnormal arrays or "bundles" of microtubules throughout the cell cycle and multiple asters of microtubules during mitosis.

Formulation

Nab-paclitaxel for injectable suspension is paclitaxel formulated as albumin-bound nanoparticles with a mean particle size of approximately 130 nanometers. Paclitaxel exists in the particles in a non-crystalline, amorphous state. Paclitaxel is a microtubule inhibitor. The chemical name for paclitaxel is 5β, 20-Epoxy-1, 2α, 4, 7β, 10β, 13α-hexahydroxytax-11-en-9-one 4, 10-diacetate 2-benzoate 13-ester with (*2R,3S*)-*N*-benzoyl-3-phenylisoserine. The empirical formula is $C_{47}H_{51}NO_{14}$ and the molecular weight is 853.19. Paclitaxel is a white to off-white crystalline powder. It is highly lipophilic, insoluble in water, and melts at approximately 216°C to 217 °C.

Nab-paclitaxel is supplied as a white to yellow, sterile, lyophilized powder for reconstitution with 20 mL of 0.9% Sodium Chloride injection, USP prior to intravenous infusion. Each single-dose vial contains 100 mg of paclitaxel (bound to human albumin) and approximately 900 mg of human albumin (containing sodium caprylate and sodium acetyltryptophanate). Each milliliter (mL) of reconstituted suspension contains 5 mg paclitaxel formulated as albumin-bound particles.

Storage

Store the vials in original cartons at 20 °C to 25 °C (68°F-77°F) and consult most current package insert for storage condition.

Stability

Consult the package insert for the most current and complete information.

Preparation

Preparation should be followed per package insert.

Administration

Do Not Substitute for or with other Paclitaxel formulations.

Prepared nab-paclitaxel should be administered intravenously over 30 minutes. Closely monitor the infusion site for extravasation or drug infiltration during administration. Limiting the infusion of nab-paclitaxel to 30 minutes may reduce the risk of infusion-related reactions.

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 or induce either CYP2C8 or CYP3A4.

Pharmacokinetics

The pharmacokinetics of total paclitaxel following 30- and 180-minute infusions of nab-paclitaxel at dose levels of 80 to 375 mg/m2 (0.31 to 1.15 times the maximum approved recommended dosage) were determined in clinical studies. Following intravenous administration of nab-paclitaxel to patients with solid tumors, paclitaxel plasma concentrations declined in a biphasic manner, the initial rapid decline representing distribution to the peripheral compartment and the slower second phase representing drug elimination.

Distribution Following nab-paclitaxel administration to patients with solid tumors, paclitaxel is evenly distributed into blood cells and plasma and is highly bound to plasma proteins (94%). The total volume of distribution is approximately 1741 L; the large volume of distribution indicates extensive extravascular distribution and/or tissue binding of paclitaxel. In a within-patient comparison study, the fraction of unbound paclitaxel in plasma was significantly higher with nab-paclitaxel (6.2%) than with solvent-based paclitaxel (2.3%). This contributes to significantly higher exposure to unbound paclitaxel with nab-paclitaxel compared with solvent-based paclitaxel, when the total exposure is comparable. In vitro studies of binding to human serum proteins, using paclitaxel concentrations ranging from 0.1 to 50 µg/mL, indicated that the presence of cimetidine, ranitidine, dexamethasone, or diphenhydramine did not affect protein binding of paclitaxel.

Metabolism In vitro studies with human liver microsomes and tissue slices showed that paclitaxel in nab-paclitaxel was metabolized primarily to 6α-hydroxypaclitaxel by CYP2C8; and to two minor metabolites, 3′-p-hydroxypaclitaxel and 6α, 3′-p-dihydroxypaclitaxel, by CYP3A4. In vitro, the metabolism of paclitaxel to 6α-hydroxypaclitaxel was inhibited by a number of agents (ketoconazole, verapamil, diazepam, quinidine, dexamethasone, cyclosporin, teniposide, etoposide, and vincristine), but the concentrations used exceeded those found in vivo following normal therapeutic doses. Testosterone, 17α-ethinyl estradiol, retinoic acid, and quercetin, a specific inhibitor of CYP2C8, also inhibited the formation of 6α-hydroxypaclitaxel in vitro. The pharmacokinetics of paclitaxel may also be altered in vivo as a result of interactions with compounds that are substrates, inducers, or inh***ibitors of CYP2C8 and/or CYP3A4.***

Elimination At the clinical dose range of 80 to 300 mg/m^2 (0.31 to 1.15 times the maximum approved recommended dosage), the mean total clearance of paclitaxel ranges from 13 to 30 L/h/m2 and the mean terminal half-life ranges from 13 to 27 hours.

Adverse Events

Consult the package insert for the most current and complete information.

The most common adverse reactions (≥ 20%) with single-agent use of nab-paclitaxel 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.

The most common adverse reactions (≥ 20%) of nab-paclitaxel in combination with carboplatin for non-small cell lung cancer are anemia, neutropenia, thrombocytopenia, alopecia, peripheral neuropathy, nausea, and fatigue. The most common serious adverse reactions of nab-paclitaxel in combination with carboplatin for non-small cell lung cancer are anemia (4%) and pneumonia (3%). The most common adverse reactions resulting in permanent discontinuation of nab-paclitaxel are neutropenia (3%), thrombocytopenia (3%), and peripheral neuropathy (1%). The most common adverse reactions resulting in dose reduction of nab-paclitaxel are neutropenia (24%), thrombocytopenia (13%), and anemia (6%). The most common adverse reactions leading to withholding or delay in nab-paclitaxel dosing are neutropenia (41%), thrombocytopenia (30%), and anemia (16%).

In a randomized open-label trial of nab-paclitaxel in combination with gemcitabine for pancreatic adenocarcinoma, the most common (≥ 20%) selected (with a ≥ 5% higher incidence) adverse reactions of nab-paclitaxel are neutropenia, fatigue, peripheral neuropathy, nausea, alopecia, peripheral edema, diarrhea, pyrexia, vomiting, decreased appetite, rash, and dehydration. The most common serious adverse reactions of nab-paclitaxel (with a ≥ 1% higher incidence) are pyrexia (6%), dehydration (5%), pneumonia (4%), and vomiting (4%). The most common adverse reactions resulting in permanent discontinuation of nab-paclitaxel are peripheral neuropathy (8%), fatigue (4%), and thrombocytopenia (2%). The most common adverse reactions resulting in dose reduction of nab-paclitaxel are neutropenia (10%) and peripheral neuropathy (6%). The most common adverse reactions leading to withholding or delay in nab-paclitaxel dosing are neutropenia (16%), thrombocytopenia (12%), fatigue (8%), peripheral neuropathy (15%), anemia (5%), and diarrhea (5%).

Nursing Guidelines

Abraxane is not known to cause the hypersensitivity reactions that Taxol does, secondary to the fact that Abraxane lacks the Cremophor EL solvent of regular paclitaxel solution, therefore premedication is not necessary. However, the patient should still be monitored closely and the infusion stopped if acute reactions occur (chest pain, back pain, flushing, diaphoresis, dyspnea, pruritus, hypotension, hypertension, bronchospasm, and/or urticaria).

Approximately 0-40% of patients may experience some degree of peripheral sensory neuropathy (numbness, tingling, burning pain, fine motor skills impairment, paresthesia, distal sensory loss) depending on the dose and schedule used. Patients receiving higher doses at shorter infusion times are at greater risk. Most cases have been reported at doses >170 mg/m2/day and with cumulative doses over multiple courses of therapy. The nerve damage may take days to months to resolve.

Mucositis can usually be managed with a salt and soda mouthwash (1 tsp. Salt, 1 tsp. Soda and 1-quart boiled water) or try OTC oral Lysine or Vitamin E.

Narcotics and nonsteroidal anti-inflammatory drugs may be used to manage the myalgias.

Monitor CBC closely. Neutropenia is most severe in patients who have had previous chemotherapy. Instruct patient to report signs or symptoms of infection, unusual bruising or bleeding to the health care team.

Monitor liver function tests

Inform patient about total alopecia

Abraxane has not been tested in combination with anthracyclines, and it is not known if there is an increased risk of cardiotoxocity.

Monitor IV site closely and establish patency before administration, it is uncertain whether Abraxane is an irritant as Taxol is.

Use in caution and employ additional monitoring in patients >75 years of age, as increased incidence of adverse events were observed in this age group.

Avoid the use of live vaccines for 3 months after last dose of nab-paclitaxel.

Warn patients of the possibility of radiation recall.

10.3 Cisplatin (NSC #119875)

Procurement

Cisplatin is not provided for the trial and institutional pharmacy shall obtain supplies from normal commercial supply chain or wholesaler.

Consult the package insert for the most current and complete information.

The main mechanism of the cytotoxic action involves the binding of cisplatin to genomic DNA in the cell nucleus to form interstrand and intrastrand cross-links. This interferes with normal transcription and/or DNA replication mechanisms and triggers cytotoxic processes that lead to cell death

Formulation

Cisplatin for injection, USP, a platinum-based drug for intravenous use, is a white to light yellow lyophilized powder. Each vial of Cisplatin for injection, USP contains 50 mg cisplatin, 450 mg Sodium Chloride, USP, and 500 mg Mannitol, USP. Cisplatin, the active ingredient in Cisplatin for injection, USP, is a yellow to orange crystalline powder with the molecular formula Cl2H6N2Pt and a molecular weight of 300.05. Cisplatin is a heavy metal complex containing a central atom of platinum surrounded by two chloride atoms and two ammonia molecules in the cis position. It is soluble in water or saline at 1 mg/mL and in dimethylformamide at 24 mg/mL. It has a melting point of 207°C.

Storage

Store at 20°C to 25°C (68°F to 77°F); excursions permitted to 15°C to 30°C (59°F to 86°F). Prior to reconstitution, store in original carton to protect from light.

Stability

Consult the package insert for the most current and complete information.

Preparation

Do not use needles or intravenous sets containing aluminum parts that can come in contact with cisplatin for injection during preparation or administration. Aluminum reacts with cisplatin for injection, causing precipitate formation and a loss of potency. Cisplatin for injection is a cytotoxic drug. Follow applicable special handling and disposable procedures.

For preparation, please consult the package insert for the most current and complete information.

Administration

Patients treated with cisplatin for injection must receive appropriate pre-treatment hydration. Maintain adequate hydration and urinary output for 24 hours after cisplatin for injection administration. Administer pre-treatment and post-treatment antiemetics as appropriate per institutional practice.

Administer cisplatin by slow intravenous infusion per institutional practice.

Drug Interactions

Simultaneous cranial irradiation, treatment with other ototoxic drugs and renal impairment may increase the risk of ototoxicity.

Pharmacokinetics

Distribution Cisplatin dose not undergo the instantaneously and reversible binding to plasma protein that is characteristic of normal drug-protein binding. Platinum from cisplatin, but not cisplatin itself, becomes bound to several plasma proteins, including albumin, transferrin, and gamma globulin. Three hours after a bolus injection and 2 hours after the end of a 3-hour infusion, 90% of the plasma platinum is protein bound. The complexes between albumin and the platinum from cisplatin do not dissociate to a significant extent and are slowly eliminated with a minimum halflife of 5 days or more. Following cisplatin doses of 20 mg/m2 to 120 mg/m2 , platinum is present in tissues for as long as 180 days after the last administration. With the exception of intracerebral tumors, platinum concentrations in tumors are generally somewhat lower than the concentrations in the organ where the tumor is located. Hepatic metastases have the highest platinum concentrations, but these are similar to the platinum concentrations in normal liver. Maximum red blood cell concentrations of platinum are reached within 90 to 150 minutes after a 100 mg/m2 dose of cisplatin and decline in a biphasic manner with a terminal half-life of 36 to 47 days.

Metabolism The chlorine atoms of cisplatin are more subject to chemical displacement reactions by nucleophiles, such as water or sulfhydryl groups, than to enzyme-catalyzed metabolism. At physiological pH, the predominant molecular species are cisplatin and monohydroxymonochloro cis-diamine platinum (II) in nearly equal concentrations. The latter, combined with the possible direct displacement of the chlorine atoms by sulfhydryl groups of amino acids or proteins, accounts for the instability of cisplatin in biological matrices. The ratios of cisplatin to total free (ultrafilterable) platinum in the plasma vary considerably between patients and range from 0.5 to 1.1 after a dose of 100 mg/m2.

Elimination Over a dose range of 40 mg to 140 mg cisplatin per m2 given as a bolus injection or as infusions varying in length from 1 hour to 24 hours, from 10% to about 40% of the administered platinum is excreted in the urine in 24 hours. Over 5 days following administration of 40 mg/m2 to 100 mg/m2 doses given as rapid, 2- to 3-hour or 6- to 8-hour infusions, a mean of 35% to 51% of the dosed platinum is excreted in the urine. Similar mean urinary recoveries of platinum of about 14% to 30% of the dose are found following 5 daily administrations of 20 mg/m2 per day, 30 mg/m2 per day, or 40 mg/m2 per day. Only a small percentage of the administered platinum is excreted beyond 24 hours post-infusion and most of the platinum excreted in the urine in 24 hours is excreted within the first few hours. The parent compound, cisplatin, is excreted in the urine and accounts for 13% to 17% of the dose excreted within 1 hour after administration of 50 mg/m2. The mean renal clearance of cisplatin exceeds creatinine clearance and was 62 mL/min per m2 and 50 mL/min per m2 following administration of 100 mg/m2 as 2-hour or 6- to 7-hour infusions, respectively. Plasma concentrations of the parent compound, cisplatin, decrease monoexponentially with a half-life of about 20 to 30 minutes following bolus administrations of 50 mg/m2 or 100 mg/m2 doses. Monoexponential decreases and plasma half-lives of about 0.5 hour are also seen following 2-hour or 7-hour infusions of 100 mg/m2. After the latter, the total body clearances and volumes of distribution at steady-state for cisplatin are about 15 Liters per hour per m2 to 16 Liters per hour per m2 and 11 Liters per m2 to 12 Liters per m2. The renal clearance of free (ultrafilterable) platinum also exceeds the glomerular filtration rate, indicating that cisplatin or other platinum-containing molecules are actively secreted by the kidneys. The renal clearance of free platinum is nonlinear and variable and is dependent on dose, urine flow rate, and individual variability in the extent of active

secretion and possible tubular reabsorption. No significant relationships exist between the renal clearance of either free platinum or cisplatin and creatinine clearance.

Adverse Events

Common adverse reactions are nephrotoxicity, peripheral neuropathy, nausea and vomiting myelosuppression, and ototoxicity. For detailed information, consult the package insert for the most current and complete information.

Nursing Guidelines

Headache may occur. Advise patient that analgesics such as Tylenol may help. Instruct patient to report any headache that is unrelieved.

Observe for sensitization reaction (rash, hives, pruritis, facial flushing, and wheezing).

May potentiate the toxic effects of fluropyrimidine (5-FU) therapy, resulting in increased hematologic and gastrointestinal (diarrhea, stomatitis) adverse effects. Monitor closely.

May cause mild nausea or upset stomach. Administer antiemetics if necessary and evaluate for their effectiveness.

If Leucovorin is being used as rescue for high dose methotrexate, does must be given on time. Impress this to the patient. If patient is taking oral Leucovorin at home and is unable to take secondary to nausea, instruct patient to notify the health care team immediately to arrange for other methods of administration.

10.4 Gemcitabine (NSC #613327)

Procurement

Gemcitabine is not provided for the trial and institutional pharmacy shall obtain supplies from normal commercial supply chain or wholesaler.

Consult the package insert for the most current and complete information.

Gemcitabine kills cells undergoing DNA synthesis and blocks the progression of cells through the G1/S-phase boundary. Gemcitabine is metabolized by nucleoside kinases to diphosphate (dFdCDP) and triphosphate (dFdCTP) nucleosides. Gemcitabine diphosphate inhibits ribonucleotide reductase, an enzyme responsible for catalyzing the reactions that generate deoxynucleoside triphosphates for DNA synthesis, resulting in reductions in deoxynucleotide concentrations, including dCTP. Gemcitabine triphosphate competes with dCTP for incorporation into DNA. The reduction in the intracellular concentration of dCTP by the action of the diphosphate enhances the incorporation of gemcitabine triphosphate into DNA (selfpotentiation). After the gemcitabine nucleotide is incorporated into DNA, only one additional nucleotide is added to the growing DNA strands, which eventually results in the initiation of apoptotic cell death.

Formulation

Gemcitabine for injection, USP is a nucleoside metabolic inhibitor that exhibits antitumor activity. Gemcitabine HCl is 2´-deoxy-2´,2´-difluorocytidine monohydrochloride (β-isomer). The empirical formula for gemcitabine HCl is C9H11F2N3O4 • HCl. It has a molecular weight of 299.66. Gemcitabine HCl is soluble in water, slightly soluble in methanol, and practically insoluble in ethanol and polar organic solvents. Gemcitabine is supplied in a sterile form for intravenous use only.

Consult the package insert for the most current and complete information for vial size.

Storage

Store at controlled room temperature 20°C to 25°C (68°F to 77°F); excursions permitted between 15°C and 30°C (59°F and 86°F)

Stability

Consult the package insert for the most current and complete information for vial size.

Preparation

Consult the package insert for the most current and complete information for vial size.

Administration

Prior to administration, dilute the reconstituted solution with 0.9% Sodium Chloride Injection, USP to a minimum final concentration of at least 0.1 mg/mL and administer over 30 – 40 minutes by intravenous infusion per institutional practice.

Drug Interactions

No drug interaction studies have been conducted.

Pharmacokinetics

Absorption and Distribution The pharmacokinetics of gemcitabine were examined in 353 patients, with various solid tumors. Pharmacokinetic parameters were derived using data from patients treated for varying durations of therapy given weekly with periodic rest weeks and using both short infusions (<70 minutes) and long infusion (70 to 285 minutes). The total gemcitabine dose varied from 500 to 3600 mg/m^2. The volume of distribution was increased with infusion length. Volume of distribution of gemcitabine was 50 L/m^2 following infusions lasting <70 minutes. For long infusions, the volume of distribution rose to 370 L/m^2. Gemcitabine pharmacokinetics are linear and are described by a 2-compartment model. Population pharmacokinetic analyses of combined single and multiple dose studies showed that the volume of distribution of gemcitabine was significantly influenced by duration of infusion and gender. Gemcitabine plasma protein binding is negligible.

Metabolism Gemcitabine disposition was studied in 5 patients who received a single 1000 mg/m2 /30 minute infusion of r***adiolabeled drug. Within one*** week, 92% to 98% of the dose was recovered, almost entirely in the urine. Gemcitabine (<10%) and the inactive uracil metabolite, 2´-deoxy-2´,2´-difluorouridine (dFdU), accounted for 99% of the excreted dose. The metabolite dFdU is also found in plasma. The active metabolite, gemcitabine triphosphate, can be extracted from peripheral blood mononuclear cells. The half-life of the terminal phase for gemcitabine triphosphate from mononuclear cells ranges from 1.7 to 19.4 hours.

Elimination Clearance of gemcitabine was affected by age and gender. The lower clearance in women and the elderly results in higher concentrations of gemcitabine for any given dose. Differences in either clearance or volume of distribution based on patient characteristics or the duration of infusion result in changes in half-life and plasma concentrations. Table 10 shows plasma clearance and half-life of gemcitabine following short infusions for typical patients by age and gender. Gemcitabine half-life for short infusions ranged from 42 to 94 minutes, and the value for long infusions varied from 245 to 638 minutes, depending on age and gender, reflecting a greatly increased volume of distribution with longer infusions.

Adverse Events

The following adverse reactions have been identified during post-approval use of gemcitabine.

Cardiovascular — Congestive heart failure, myocardial infarction, Arrhythmias, supraventricular arrhythmias.
Vascular Disorders — Peripheral vasculitis, gangrene, and capillary leak syndrome
Skin — Cellulitis, severe skin reactions, including desquamation and bullous skin eruptions
Hepatic — Hepatic failure, hepatic veno-occlusive disease
Pulmonary — Interstitial pneumonitis, pulmonary fibrosis, pulmonary edema, and adult respiratory distress syndrome (ARDS)
Nervous System — Posterior reversible encephalopathy syndrome (PRES)
Detailed information, consult the package insert for the most current and complete information.

Nursing Guidelines

Monitor CBC, differential, PLTs prior to each dose. Myelosuppression is the principal dose-limiting factor. Modification may be considered by physician when bone marrow suppression is suspected.

Evaluate hepatic and renal function prior to initiation of therapy and periodically thereafter. Closely observe those patients with a history of preexisting mild renal impairment or hepatic insufficiency. Encourage hydration.

GEMZAR clearance is affected by age and gender. Grade 3/4 thrombocytopenia has been more common in elderly women.

Antiemetics may be required for probable mild to moderate nausea and vomiting. Assess for their effectiveness.

Instruct patient in management of possible mild diarrhea and stomatitis.

GEMZAR may cause fever in the absence of clinical infection. Fever can be accompanied by other flu-like symptoms. Instruct patient to report fever or flu-like symptoms to healthcare team. Treat symptoms as they occur.

Macular or finely granular maculopapular eruptions were experienced by 30% of patients tested. Instruct patients to report any skin changes.

Instruct patient to report any respiratory changes.

Burning may occur at the injection site. May apply heat during infusion to minimize pain.

11.0 MEASUREMENT OF EFFECT

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) guidelines (version 1.1). Changes in the largest diameter (unidimensional measurement) of the tumor lesions and the short axis measurements in the case of lymph nodes are used in the RECIST guideline [11].

11.1 Schedule of Evaluations:

For the purposes of this study, patients should be reevaluated every 8 weeks.

11.2 Definitions of Measurable and Non-Measurable Disease

11.21 Measurable Disease

11.211 A non-nodal lesion is considered measurable if its longest diameter can be accurately measured as ≥2.0 cm with chest x-ray, or as ≥1.0 cm with CT scan, CT component of a PET/CT, or MRI.

11.212 A superficial non-nodal lesion is measurable if its longest diameter is ≥ 1.0 cm in diameter as assessed using calipers (e.g. skin nodules) or

imaging. In the case of skin lesions, documentation by color photography, including a ruler to estimate the size of the lesion, is recommended.

11.213 A malignant lymph node is considered measurable if its short axis is ≥1.5 cm when assessed by CT scan (CT scan slice thickness recommended to be no greater than 5 mm).

NOTE: A tumor lesion in a previously irradiated area will be considered measurable disease if there has been interval growth in that lesion by at least 1 cm in maximal dimension beyond one month after completion of radiation.

11.22 Non-Measurable Disease

11.221 All other lesions (or sites of disease) are considered non-measurable disease, including pathological nodes (those with a short axis ≥1.0 to <1.5 cm). Bone lesions, leptomeningeal disease, ascites, pleural/pericardial effusions, lymphangitis cutis/pulmonis, inflammatory breast disease, and abdominal masses (not followed by CT or MRI), are considered as non-measurable as well.

Note: '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. In addition, lymph nodes that have a short axis <1.0 cm are considered non-pathological (i.e., normal) and should not be recorded or followed.

11.3 Guidelines for Evaluation of Measurable Disease

11.3.1 Measurement Methods:

- All measurements should be recorded in metric notation (i.e., decimal fractions of centimeters) using a ruler or calipers.
- The same method of assessment and the same technique must be used to characterize each identified and reported lesion at baseline and during follow-up. For patients having only lesions measuring at least 1 cm to less than 2 cm must use CT imaging for both pre- and post-treatment tumor assessments.
- Imaging-based evaluation is preferred to evaluation by clinical examination when both methods have been used at the same evaluation to assess the antitumor effect of a treatment.

11.32 Acceptable Modalities for Measurable Disease:

- Conventional CT and MRI: This guideline has defined measurability of lesions on CT scan based on the assumption that CT slice thickness is 5 mm or less. If CT scans have slice thickness greater than 5 mm, the minimum size for a measurable lesion should be twice the slice thickness.
- As with CT, if an MRI is performed, the technical specifications of the scanning sequences used should be optimized for the evaluation of the type and site of disease. The lesions should be measured on the same pulse sequence. Ideally, the same type of scanner should be used and the image acquisition protocol should be followed as closely as possible to prior scans. Body scans should be performed with breath-hold scanning techniques, if possible.

- PET-CT: If the site can document that the CT performed as part of a PET-CT is of identical diagnostic quality to a diagnostic CT (with IV contrast), then the CT portion of the PET-CT can be used for RECIST measurements and can be used interchangeably with conventional CT in accurately measuring cancer lesions over time.
- FDG-PET: FDG-PET scanning is allowed to complement CT scanning in assessment of progressive disease [PD] and particularly possible 'new' disease. A 'positive' FDG-PET scanned lesion is defined as one which is FDG avid with an update greater than twice that of the surrounding tissue on the attenuation corrected image; otherwise, an FDG-PET scanned lesion is considered 'negative.' New lesions on the basis of FDG-PET imaging can be identified according to the following algorithm:

  a. Negative FDG-PET at baseline with a positive FDG-PET at follow-up is a sign of PD based on a new lesion.

  b. No FDG-PET at baseline and a positive FDG-PET at follow-up:

    i. If the positive FDG-PET at follow-up corresponds to a new site of disease confirmed by CT, this is PD.

    ii. If the positive FDG-PET at follow-up is not confirmed as a new site of disease on CT at the same evaluation, additional follow-up CT scans (i.e., additional follow-up scans at least 4 weeks later) are needed to determine if there is truly progression occurring at that site. In this situation, the date of PD will be the date of the initial abnormal FDG-PET scan.

    iii If the positive FDG-PET at follow-up corresponds to a pre-existing site of disease on CT that is not progressing on the basis of the anatomic images, it is not classified as PD. Additional follow-up CT scans (i.e., additional follow-up scans at least 4 weeks later) are needed to determine if there is truly progression occurring at that site. In this situation, the date of PD will be the date of the initial abnormal FDG-PET scan.

11.33 Measurement at Follow-up Evaluation:

- In the case of stable disease (SD), follow-up measurements must have met the SD criteria at least once after study entry at a minimum interval of 6 weeks (see Section 11.44).
- The cytological confirmation of the neoplastic origin of any effusion that appears or worsens during treatment when the measurable tumor has met criteria for response or stable disease is mandatory to differentiate between response or stable disease (an effusion may be a side effect of the treatment) and progressive disease.

11.4 Measurement of Effect

11.41 Target Lesions & Target Lymph Nodes

- Measurable lesions (as defined in Section 11.21) up to a maximum of 5 lesions, representative of all involved organs, should be identified as "Target Lesions" and recorded and measured at baseline. These lesions can be non-

nodal or nodal (as defined in 11.21), where no more than 2 lesions are from the same organ and no more than 2 malignant nodal lesions are selected.

Note: If fewer than 5 target lesions and target lymph nodes are identified (as there often will be), there is no reason to perform additional studies beyond those specified in the protocol to discover new lesions.

- Target lesions and target lymph nodes should be selected on the basis of their size, be representative of all involved sites of disease, but in addition should be those that lend themselves to reproducible repeated measurements. It may be the case that, on occasion, the largest lesion (or malignant lymph node) does not lend itself to reproducible measurements in which circumstance the next largest lesion (or malignant lymph node) which can be measured reproducibly should be selected.
- Baseline Sum of Dimensions (BSD): A sum of the longest diameter for all target lesions plus the sum of the short axis of all the target lymph nodes will be calculated and reported as the baseline sum of dimensions (BSD). The BSD will be used as reference to further characterize any objective tumor response in the measurable dimension of the disease.
- Post-Baseline Sum of the Dimensions (PBSD): A sum of the longest diameter for all target lesions plus the sum of the short axis of all the target lymph nodes will be calculated and reported as the post-baseline sum of dimensions (PBSD). If the radiologist is able to provide an actual measure for the target lesion (or target lymph node), that should be recorded, even if it is below 0.5 cm. If the target lesion (or target lymph node) is believed to be present and is faintly seen but too small to measure, a default value of 0.5 cm should be assigned. If it is the opinion of the radiologist that the target lesion or target lymph node has likely disappeared, the measurement should be recorded as 0 cm.
- The minimum sum of the dimensions (MSD) is the minimum of the BSD and the PBSD.

11.42 Non-Target Lesions & Non-Target Lymph Nodes

Non-measurable sites of disease (Section 11.22) are classified as non- target lesions or non-target lymph nodes and should also be recorded at baseline. These lesions and lymph nodes should be followed in accord with 11.433.

11.43 Response Criteria

11.431 All target lesions and target lymph nodes followed by CT/MRI/PET-CT/Chest X-ray/physical examination must be measured on re-evaluation at evaluation times specified in Section 11.1. Specifically, a change in objective status to either a PR or CR cannot be done without re-measuring target lesions and target lymph nodes.

Note: Non-target lesions and non-target lymph nodes should be evaluated at each assessment, especially in the case of first response or confirmation of response. In selected circumstances, certain non-target organs may be evaluated less frequently. For example, bone scans may need to be repeated only when complete response is identified in target disease or when progression in bone is suspected.

11.432 Evaluation of Target Lesions

Complete Response (CR): All of the following must be true:

a. Disappearance of all target lesions.
b. Each target lymph node must have reduction in short axis to <1.0 cm.

Partial Response (PR): At least a 30% decrease in PBSD (sum of the longest diameter for all target lesions plus the sum of the short axis of all the target lymph nodes at current evaluation) taking as reference the BSD (*see* Section 11.41).

Progression (PD): At least one of the following must be true:

a. At least one new malignant lesion, which also includes any lymph node that was normal at baseline (< 1.0 cm short axis) and increased to ≥ 1.0 cm short axis during follow-up.

b. At least a 20% increase in PBSD (sum of the longest diameter for all target lesions plus the sum of the short axis of all the target lymph nodes at current evaluation) taking as reference the MSD (Section 11.41). In addition, the PBSD must also demonstrate an absolute increase of at least 0.5 cm from the MSD.

c. See Section 11.32 for details in regards to the requirements for PD via FDG-PET imaging.

Stable Disease (SD): Neither sufficient shrinkage to qualify for PR, nor sufficient increase to qualify for PD taking as reference the MSD.

11.433 Evaluation of Non-Target Lesions & Non-target Lymph Nodes

Complete Response (CR): All of the following must be true:

a. Disappearance of all non-target lesions.
b. Each non-target lymph node must have a reduction in short axis to <1.0 cm

Non-CR/Non-PD: Persistence of one or more non-target lesions or non-target lymph nodes.

Progression (PD): At least one of the following must be true:

a. At least one new malignant lesion, which also includes any lymph node that was normal at baseline (< 1.0 cm

short axis) and increased to ≥ 1.0 cm short axis during follow-up.

b. Unequivocal progression of existing non-target lesions and non-target lymph nodes. (NOTE: Unequivocal progression should not normally trump target lesion and target lymph node status. It must be representative of overall disease status change.)

c. See Section 11.32 for details in regards to the requirements for PD via FDG-PET imaging.

11.44 Overall Objective Status

The overall objective status for an evaluation is determined by combining the patient's status on target lesions, target lymph nodes, non-target lesions, non-target lymph nodes, and new disease as defined in the following tables:

For Patients with Measurable Disease

Target Lesions & Target Lymph Nodes	**Non-Target Lesions & Non-Target Lymph Nodes**	**New Sites of Disease**	**Overall Objective Status**
CR	CR	No	CR
CR	Non-CR/Non-PD	No	PR
PR	CR Non-CR/Non-PD	No	PR
CR/PR	Not All Evaluated*	No	PR**
SD	CR Non-CR/Non-PD Not All Evaluated*	No	SD
Not all Evaluated	CR Non-CR/Non-PD Not All Evaluated*	No	Not Evaluated (NE)
PD	Unequivocal PD CR Non-CR/Non-PD Not All Evaluated*	Yes or No	PD
CR/PR/SD/PD/Not all Evaluated	Unequivocal PD	Yes or No	PD

Target Lesions & Target Lymph Nodes	Non-Target Lesions & Non-Target Lymph Nodes	New Sites of Disease	Overall Objective Status
CR/PR/SD/PD/Not all Evaluated	CR Non-CR/Non-PD Not All Evaluated*	Yes	PD

*See Section 11.431

For Patients with Non-Measurable Disease Only:

Non-Target Lesions & Non-Target Lymph Nodes	New Sites of Disease	Overall Objective Status
CR	No	CR
Non-CR/Non-PD	No	Non-CR/Non-PD
Not All Evaluated*	No	Not Evaluated (NE)
Unequivocal PD	Yes or No	PD
Any	Yes	PD

*See Section 11.431

11.45 Symptomatic Deterioration: Patients with global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time, and not either related to study treatment or other medical conditions, should be reported as PD due to "symptomatic deterioration." Every effort should be made to document the objective progression even after discontinuation of treatment due to symptomatic deterioration. A patient is classified as having PD due to "symptomatic deterioration" if any of the following occur that are not either related to study treatment or other medical conditions:

- Weight loss >10% of body weight.
- Worsening of tumor-related symptoms.
- Decline in performance status of >1 level on ECOG scale.

12.0 END OF TREATMENT/INTERVENTION

12.1 Duration of Protocol Treatment

Protocol treatment (intervention) is to continue until stopped for any of the reasons listed in Section 12.2. Please see the study calendar (Section 5.0) and the treatment section (Section 7.0) for treatment and following up time periods.

12.2 Criteria for Discontinuation of Protocol Treatment/Intervention

In the absence of treatment delays due to adverse event(s), treatment may continue until one of the following criteria applies:

- Disease progression (either by radiographic criteria or symptomatic deterioration)
- Intercurrent illness that prevents further administration of treatment
- Unacceptable adverse event(s)

- Patient decides to withdraw from the study
- General or specific changes in the patient's condition render the patient unacceptable for further treatment in the judgment of the investigator
- Patient non-compliance
- Pregnancy (if applicable)
- All women of child bearing potential should be instructed to contact the investigator immediately if they suspect they might be pregnant (e.g., missed or late menstrual period) at any time during study participation.
- The investigator must immediately notify CTEP in the event of a confirmed pregnancy in a patient participating in the study.
- Termination of the study by sponsor

The reason(s) for protocol therapy discontinuation, the reason(s) for study removal, and the corresponding dates must be documented in the Case Report Form (CRF).

12.3 Follow-up

12.3.1 Duration of Follow-up:

All patients will be followed for survival for up to 2 years after the end of treatment. Refer to Study calendar in Section 5.0 for follow-up details.

12.3.2 Follow-up for Patients who Stop Study Treatment Early

Patients who are removed from protocol therapy will be followed per Section 5.0, post-treatment follow-up. Protocol treatment will be discontinued and further treatment is at the discretion of the treating physician.

12.3.4 Follow-up for Specimen Submission

If the patient discontinues study treatment for any reason, specimens should continue to be collected and submitted after discontinuation of therapy per Section 6.2.

12.4 Extraordinary Medical Circumstances

If, at any time the constraints of this protocol are detrimental to the patient's health and/or the patient no longer wishes to continue protocol therapy, protocol therapy shall be discontinued. In this event:

- Document the reason(s) for discontinuation of therapy on data forms.
- Follow the patient for protocol endpoints as required by the Study Calendar.

13.0 STATISTICAL CONSIDERATIONS

13.1 Study Endpoints

13.2.1 Primary Endpoint

- **Phase II:** The primary endpoint of phase II component of this study is overall response rate (ORR), defined as the proportion of patients who achieve complete response (CR) or partial response (PR) per RECIST v1.1 during the protocol treatment (up to 12 months if a patient receives protocol treatment longer than 12 months) among evaluable patients. Patients who are properly randomized, eligible, and started at least one dose of protocol treatment are evaluable for the phase II ORR primary endpoint. **ORR will be assessed per local investigator adjudication.**

- **Phase III:** The primary endpoint of phase III component of this study is overall survival (OS) time, defined as the time form the date of randomization to the date of death due to all causes. Patients without a recorded OS event at the time of analysis will be censored at the date of last follow-up.

13.2.2 Secondary Endpoints

- Progression-free survival (PFS): is defined as the time from the date of randomization to the date of first documented disease progression per RECIST 1.1 or death due to all causes, whichever occurs first. Patients without a recorded PFS event at the time of analysis will be censored at the date of last disease evaluation.
- Duration of response (DoR): is measured from the time that criteria are met for CR or PR (whichever status is recorded first) until the first date that recurrence or PD is objectively documented.
- CA19-9 response: is defined as a minimum 25% decrease in CA19-9 at any time point, compared to baseline measurement, in patients with a baseline CA19-9 $\geq$ 2x ULN.
- Adverse Events (AE): AEs and the maximum grade for each type of adverse events will be summarized for each patient.

13.2 Sample Size

We anticipate enrolling a maximum of 100 patients (50 per arm). BRCA1/2 or PALB2 mutations occur in about 6-9% of all cases of PDAC. In a recent SWOG second-line PDAC study, the accrual rate measured approximately 14 patients/month. With an estimated 9% rate of BRCA1/2 or PALB2 mutations, we estimate an accrual of 2patients/month for this study. The accrual period of this study is estimated to be a little over 4 years.

13.3 Power Justification

The design of this trial is a randomized, seamless phase II/III trial. After a patient is registered, they will be assigned to one of the two treatment arms in a 1:1 ratio utilizing a dynamic allocation algorithm based on the methods by Pocock and Simon [25].

The patients included in the phase II endpoints analyses will be included in the phase III endpoints analyses. The accrual will not be halted while waiting for phase II endpoints to be matured and analyzed, unless we experience unexpected rapid accrual and/or delay in obtaining ORR results data, or other unforeseen situations. If the criteria for continuation have been satisfied at conclusion of phase II portion, to protect the phase III comparison, the actual results of the phase II portion will not be released beyond the Alliance DSMB.

13.3.1 Phase II Portion

The phase II portion of this trial is designed to primarily compare ORR in patients with HR-deficient PDAC whose disease has progressed on front-line FOLFIRINOX treated with NABPLAGEM = nab-paclitaxel, gemcitabine, and cisplatin (arm 1) versus nab-paclitaxel and gemcitabine (arm 2). Several published studies using gemcitabine/nab-paclitaxel in second line following FOLFOXIRI reported ORR rates of 13%[12], 15%[13] and 17.5%[14]. Hence, we assume 15% ORR in control arm (nab-paclitaxel and gemcitabine). A sample size of 64 (32 per arm) patients will provide 84.3% power to detect an increase of 25% (i.e., 40% in experimental arm; NABPLAGEM) at one-sided alpha of 0.093.

13.3.2 Phase III Portion

Phase III portion of this trial is designed to primarily compare OS in patients with HR-deficient PDAC whose disease has progressed on front-line FOLFIRINOX treated with

NABPLAGEM = nab-paclitaxel, gemcitabine, and cisplatin (arm 1) versus nab-paclitaxel and gemcitabine (arm 2). Phase III portion implements a group sequential design with one futility interim analysis based on a binding beta spending function (Rho family with Rho=2.5), which will be performed when 50% of OS events have been observed (37 deaths). Prospective studies of second-line gemcitabine and nab-paclitaxel reported a median OS of approximately 7.6 to 9.9 months in unselected patients.[12-14]. The SWOG 1513 trial presented at ASCO 2019 reported a median overall survival of 11.9 months in the HRD subgroup. Therefore, we assume a median OS of 9 months in control arm for sample size and power calculation. A total number of **73 deaths** will provide 90% power to detect an effect size of hazard ratio (HR) = 0.5 (median OS of 18 months versus 9 months in arm 1 versus arm 2) at a one-sided alpha of 0.05. With further assumptions of an accrual rate of 2 patients per month and a minimum of 12 months of follow-up, a total of 90 patients (45 in each arm) are required per the study design , unless the study team makes a decision of early termination due to crossing futility boundary at interim OS analysis. An additional 10 patients (11% inflation) will be accrued to account for ineligible patients and patients who withdraw consent for all follow-up (i.e., early dropouts) for a total maximum enrolment of 100 patients (50 in each arm). With the decision rules stated below in Section 13.4.3, this design provides the following design operation characteristics for interim analyses:

Analyses time point	If the true median OS is …	H1 Experimental arm: 18m Control arm: 9m	H0 Experimental arm: 9m Control arm: 9m
interim analysis (futility only) at 50% of events observed	Then the probability of stopping at the interim analysis due to futility is …	0.018	0.502

13.4 Statistical Analysis Plan

13.4.1 Analysis Populations

- **Modified Intent-to-Treat (mITT) Population:** mITT population includes all patients who are deemed eligible and are properly randomized. The treatment grouping will be according to the original assignment at randomization.
- **Per-Protocol (PP) Population:** PP population includes all patients who are deemed eligible, properly randomized, and received at least one dose of protocol defined treatment. The treatment grouping will be according to the actual treatment received during the first cycle (i.e. first month after randomization).
- **Safety Population:** Safety population includes all patient who received any dose of treatment defined by protocol.

13.4.2 Primary Endpoints – Phase II Portion

The primary endpoint (ORR) analysis will be conducted based on the first 32 patients in each arm who meet PP population criteria (see section 13.4.1). If the difference in ORR between experimental and control arm is > 0.138 (or one-sided p-value <0.1), then we conclude that the experimental treatment improves ORR and the trial will continue to phase III portion. Otherwise, we will terminate the study accrual.

13.4.3 Primary Endpoints – Phase III Portion

The primary endpoint analysis will be conducted on modified intention-to-treat population (see section 13.4.1). At interim and final analyses, stratified Cox model will be conducted to compare OS in the experimental arm to OS in the control arm with stratification factors as stratum, based on all data collected at the analysis time point.

- Interim Analysis Decision Rule: The interim analysis will be conducted when 50% of targeted events (about 37 deaths) which is estimated around 30 to 36 months after the first patient is randomized (about 60 to 72 patients accrued). If the observed HR (stratified by stratification factors) at interim analysis is > 1.008, we will conclude that the chance of OS in experimental arm being superior to that in control arm is too low to continue the study and the accrual will be terminated. Otherwise, the study will continue to full accrual of the phase III portion.
  Accrual will continue during the interim analysis phase unless we observe a much higher rate than expected accrual rate or toxicity rate.

- Final Analysis Decision Rule: If the trial continues after the interim analysis, the final OS analysis will be performed when 100% of the events (73 deaths) are observed combining the two arms. Stratified Cox model will be conducted to compare OS in the experimental arm to OS in the control arm. If the one-sided p-value of the comparison is < 0.05, then we will conclude the OS in the experimental arm is superior to the control arm.

13.4.4 Secondary Endpoints

Detailed statistical analysis plan will be developed prior to the final analysis of Phase III primary endpoint. The analyses of secondary endpoints will be conducted on mITT, PP and safety population whenever it is applicable and plausible. The distributions of time-to-event endpoints (PFS and DoR) will be estimated, in each arm, using the method of Kaplan-Meier and compared by stratified Cox regression model. The maximum grade for each type of adverse events that are possibly, probably, or definitely related to study treatments will be recorded for each patient. The frequency tables will be reviewed to determine the patterns. Binary endpoints (CA19-9 response) will be summarized by proportions and 95% exact binomial confidence intervals in each arm and compared between the pairs of treatment groups using Chi-square test (or Fisher's exact test if the data in contingency table is sparse). Multiple comparison adjustments will be applied when it is applicable.

Pre-planned subgroup analyses include evaluating primary and key secondary endpoints within:

- Best response to first-line treatment (SD vs PR vs primary platinum resistance).
- Prior receipt of maintenance PARP inhibitor therapy
- A sensitivity analysis will also be performed using only eligible patients characterized as platinum-resistant (defined as disease progression on or within 12 weeks of last platinum dose). The primary statistical methods will be consistently applied in this analysis to ensure comparability of results.

13.5 Monitoring

13.5.1 Safety Monitoring

The safety monitoring rule specified below is based on the knowledge available at study development. We note that the Adverse Event Monitoring Rule may be adjusted in the event of either 1) the study re-opening to accrual or 2) at any time during the conduct of the trial and in consideration of newly acquired information regarding the adverse event profile of the treatment(s) under investigation.

If at any time in **either arm, separately,** we observe at least one of the following, discussions between the Study Team, Alliance DSMB, and NCI are required to assess if any changes to the study are needed:

- If more than 2 patients in the first 10 treated patients (or > 20% of all patients after 10 are accrued), within each arm separately, experience a grade 4 or higher non-hematologic adverse event deemed at least possibly related to study treatment (i.e. an adverse event with attribute specified as "possible," "probable," or "definite").

The Study Chair and the Study Statistician will review the study monthly to identify accrual, adverse event/safety, and any endpoint problems that might be developing.

13.5.2 Data and Safety Monitoring Board

This study will be monitored by the Alliance Data and Safety Monitoring Board (DSMB), an NCI-approved functioning body. Reports containing efficacy, adverse event, and administrative information will be provided to the DSMB every six months as per NCI guidelines

13.5.3 Data Mapping Utility (DMU)

This study has been assigned Demography monitoring.

Required submission of patient demographic data for this study will be submitted automatically via OPEN.

Note: Serious adverse events must be submitted via CTEP-AERS per protocol guidelines.

13.6 Inclusion of Women and Minorities

This study will be available to all eligible patients, regardless of race, gender, or ethnic origin. There is no information currently available regarding differential effects of this regimen in subsets defined by race, gender, or ethnicity, and there is no reason to expect such differences to exist. Therefore, although the planned analysis will, as always, look for differences in treatment effect based on racial and gender groupings, the sample size is not increased in order to provide additional power for subset analyses.

The geographical region served by the Alliance, has a population which includes approximately 18% minorities. Based on prior Alliance studies involving similar disease sites, we expect about 25% of patients will be classified as minorities by race and about 47% of patients will be women. Expected sizes of racial by gender subsets for patients registered randomized to this study are shown in the following table.

DOMESTIC PLANNED ENROLLMENT REPORT					
Racial Categories	**Ethnic Categories**				**Total**
	Not Hispanic or Latino		**Hispanic or Latino**		
	Female	**Male**	**Female**	**Male**	

DOMESTIC PLANNED ENROLLMENT REPORT					
American Indian/ Alaska Native	0	0	0	0	0
Asian	6	3	0	0	9
Native Hawaiian or Other Pacific Islander	0	0	0	0	0
Black or African American	8	9	0	0	17
White	31	38	2	3	74
More Than One Race	0	0	0	0	0
Total	450	50	2	3	100

13.7 Other Pre-Specified Outcomes: NIH-Required Analyses

Estimates of treatment effect and the corresponding 95% confidence intervals (CIs) will be provided as follows (with an understanding that sometimes the CI or estimate will not be computable because of scant data).

- Estimates of ORR and OS and the corresponding 95% confidence intervals (CIs) by sex.
- Estimates of ORR and OS and the corresponding 95% confidence intervals (CIs) by race.
- Estimates of ORR and OS and the corresponding 95% confidence intervals (CIs) by ethnicity.

14.0 CORRELATIVE AND COMPANION STUDIES

There will be optional biobanking for future correlative studies, and all patients are encouraged to participate.

14.1 Biobanking for Future Correlative Science Studies

This is optional for patients to participate. The optional tissue and blood collection for future studies (for example, ctDNA analysis to look for secondary BRCA reversion mutations) must be offered to all patients enrolled on Alliance A0**22106** (although patients may opt to not participate). Testing of banked specimens will not occur until an amendment to this treatment protocol (or separate correlative science protocol) is reviewed and approved in accordance with National Clinical Trials Network (NCTN) policies.

15.0 CONTINUITY OF CARE, MONITORING PLAN, AND REGULATORY CONSIDERATIONS

15.1 IRB terminations

Until institutions receive a formal notice from the Alliance regarding termination to patient follow-up, institutions must not close this trial with the IRB of record for the study. Please contact the Alliance Regulatory team at regulatory@alliancenctn.org with any questions.

15.2 Monitoring Plan

Standard Alliance monitoring procedures will be used for this study.

15.3 Continuity of Care

Continuity of Care Provided by Non-Research Staff: The Responsible Investigator for a patient already enrolled on a clinical trial may make appropriate arrangements with a Local

Healthcare Provider to provide certain study activities in order to provide continuity of care and follow-up study visits when the patient cannot travel to the site location of the Responsible Investigator. In this situation, the Local Healthcare Provider is providing intermittent/short-term care and the Responsible Investigator believes it is in the patient's best interest to continue study activities. The activities provided by the Local Healthcare Provider must be conducted under the oversight of the Responsible Investigator in accordance with the protocol and with assurances that processes are in place to report all required information to the Responsible Investigator who is responsible for ensuring that the data is entered into the data management system for the trial. These activities include the following:

- Protocol required physical exam(s) and assessment of the patient's vital signs, temperature, weight, performance status, and other standard assessments may be conducted by the Local Healthcare Provider. All clinical findings and information must be conveyed to the Responsible Investigator overseeing the patient's care in the trial. All decisions must continue to reside with the Responsible Investigator for the patient's care within the trial.
- Protocol specified clinical laboratory tests may be performed by the Local Healthcare Provider/Local Laboratory with results sent to the Responsible Investigator.
- Protocol required blood collections necessary for patient assessment within the clinical trial that require evaluation in a central research laboratory may also be collected by the Local Healthcare Provider and shipped to the designated central laboratory under the Responsible Investigator's oversight. The Responsible Investigator needs to ensure that the Local Healthcare Provider can make these collections depending on the protocol requirements.
- Protocol required standard parameters such as ECHO and radiologic imaging may be performed locally with results sent to the Responsible Investigator for review (report and image, if applicable).
- Drug therapy with non-investigational agents may be administered by the Local Healthcare Provider (this includes therapy on treatment arms that do not include investigational agents on IND trials) with appropriate reporting of study therapy administration data and adverse event information to the Responsible Investigator. Standard radiation therapy, surgery, and other interventions that do not require protocol-specified credentialing may also be performed by the Local Healthcare Provider with oversight by the Responsible Investigator. In such cases, for this activity, the Responsible Investigator must inform the IRB of record for the trial that a Local Healthcare Provider is providing study therapy under his/her oversight. For trials under the NCI CIRB, the Responsible Investigator can send a simple email notification to the NCI CIRB at ncicirbcontact@emmes.com. For trials not under the NCI CIRB, the Responsible Investigator should follow the appropriate local IRB notification policy.

These activities performed locally are part of usual oncology care and are being provided only on an intermittent/short-term basis with direct oversight by the Responsible Investigator with respect to protocol requirements. All decisions on care within the clinical trial are made by the Responsible Investigator. In this situation, these activities are not considered protocol deviations simply because they are being performed locally and not directly by the Responsible Investigator. The Responsible Investigator is still required to report any protocol deviations and unanticipated problems that occurs (e.g., non-compliance with protocol therapy) per standard procedures.

New Patient Enrollment: Patients can only be enrolled on a clinical trial at an active site that is participating in the study. The active participating sites for a trial can be found on the members side of the CTSU website at: https://www.ctsu.org/public/default_login.aspx.

16.0 GENERAL REGULATORY CONSIDERATIONS AND CREDENTIALING

There are no credentialing requirements for this trial.

17.0 REFERENCES

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