NRG ONCOLOGY

RTOG 1201

A PHASE II RANDOMIZED TRIAL EVALUATING THE ADDITION OF HIGH OR STANDARD INTENSITY RADIATION TO GEMCITABINE AND NAB-PACLITAXEL FOR LOCALLY ADVANCED PANCREATIC CANCER

This trial is part of the National Clinical Trials Network (NCTN) program, which is sponsored by the National Cancer Institute (NCI). The trial will be led by NRG Oncology with the participation of the network of NCTN organizations: the Alliance for Clinical Trials in Oncology; ECOG-ACRIN Cancer Research Group; and SWOG.

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Protocol Agent (7/31/14)

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Participating Sites (7/31/14)

- U.S. [ ]
- Canada Only [ ]
- U.S. and Canada [ ]
- Approved International Member Sites [ ]

Document History

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NRG Oncology

1-800-227-5463, ext. 4189

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A PHASE II RANDOMIZED TRIAL EVALUATING THE ADDITION OF HIGH OR STANDARD INTENSITY RADIATION TO GEMCITABINE AND NAB-PACLITAXEL FOR LOCALLY ADVANCED PANCREATIC CANCER

SCHEMA (7/31/14)

**STEP 1 REGISTRATION**

Gemcitabine + nab-Paclitaxel x 3 cycles (total of 9 doses)

**Central SMAD4 TESTING**

Mandatory submission of a cell block or core biopsy

*NOTE:* Tumor tissue must be received and central review completed before STEP 2 randomization can occur

**CT/MRI of abdomen/pelvis for restaging**

**STEP 2 REGISTRATION- for non-progressing patients**

Stratify: CA19-9 (< 1 vs. ≥ 1 to ≤ 90 vs. > 90);
SMAD4 (intact vs. loss. vs. undetermined)

**RANDOMIZE**

**Arm 1**

Gemcitabine + nab-Paclitaxel x 1 cycle (4 weeks)

63.0 Gy in 28 fractions (IMRT), capecitabine

Gemcitabine + nab-Paclitaxel until progression

**Arm 2**

Gemcitabine + nab-Paclitaxel x 1 cycle (4 weeks)

50.4 Gy in 28 fractions (3D-CRT or IMRT), capecitabine

Gemcitabine + nab-Paclitaxel until progression

**Arm 3**

Gemcitabine + nab-Paclitaxel until disease progression

No chemoradiation

See pre-registration requirements in Section 5.0.
See Section 7.0 for details/doses of study drug.

Patient Population: (See Section 3.0 for Eligibility)

Histopathological or cytological diagnosis of adenocarcinoma of the pancreas; tumor diameter ≤ 7 cm, unresectable by radiographic criteria (pancreas protocol CT or MRI) or exploration, no distant metastases, A cell block or core biopsy must be submitted for central review and analysis of SMAD4 status as soon as possible following step 1 registration; See Section 10.2 for details of tissue submission

Required Sample Size: 288 randomized; project 346 entered
1. Does the patient have histologically or cytologically proven diagnosis of adenocarcinoma of the pancreas prior to step 1 registration?

2. Is the tumor diameter ≤ 7cm?

3. Is the tumor unresectable by radiographic criteria (pancreas protocol CT or MRI) or exploration within 30 days prior to step 1 registration?

4. Will a cell block or core biopsy be submitted for central review and analysis of SMAD4 status?

5. Was a History/physical examination performed within 30 days prior to step 1 registration?

6. Did the patient have a whole body FDG-PET/CT or CT of the chest and CT or MRI of the abdomen and pelvis (if not already included in pancreas protocol study) within 30 days prior to step 1 registration?

7. Is the Zubrod Performance Status 0-1 within 30 days prior to step 1 registration?

8. Age ≥ 18?

9. Did all blood work meet the requirements, per Section 3.1 of the protocol, including the CA19-9 needed for stratification?

10. Is the patient a woman of childbearing potential?

   If yes, was there a negative serum pregnancy test within 30 days prior to step 1 registration?

   Does she agree to practice adequate contraception?

11. Is the patient a male?

   If yes, does he agree to practice adequate contraception?

12. Did the patient provide study specific informed consent prior to study entry?

13. Has the patient had a prior invasive malignancy (except non-melanomatus skin cancer and early prostate cancer that had a non-rising PSA)?

   If yes, has the patient been disease free for a minimum of 1095 days (3 years)?

14. Prior systemic anti-cancer therapy for pancreatic cancer?

15. Prior radiation therapy to the abdomen that would result in overlap of the radiation therapy fields?

16. Does the patient have any of the severe, active comorbidities, as defined in Section 3.2.5 of the protocol?

17. Prior allergic reaction to the study drug(s) involved in this protocol?
ELIGIBILITY CHECKLIST - STEP 1 (6/25/13)  
(page 2 of 3)

NRG Oncology Institution #  
RTOG 1201  
Case #

____ (N)  18. Is there a pre-existing ≥ grade 2 neuropathy?  
____ (N)  19. Is there more than one primary tumor?  
____ (N)  20. Does the patient have distant metastases?

The following questions will be asked at Study Registration for STEP 1:  
IMRT CREDENTIALING IS REQUIRED BEFORE REGISTRATION

________  1. Institutional person randomizing case.  
________ (Y)  2. Has the Eligibility Checklist been completed?  
________ (Y)  3. In the opinion of the investigator, is the patient eligible?  
________  4. Date informed consent signed  
________  5. Patient’s Initials (Last First Middle)  
________  6. Verifying Physician  
________  7. Patient ID  
________  8. Date of Birth  
________  9. Race  
________ 10. Ethnicity  
________ 11. Gender  
________ 12. Country of Residence  
________ 13. Zip Code (U.S. Residents)  
________ 14. Method of Payment  
________ 15. Any care at a VA or Military Hospital?  
________ 16. Calendar Base Date  
________ 17. Registration date  
________ 18. Medical Oncologist’s Name
ELIGIBILITY CHECKLIST - STEP 1 (6/25/13)

NRG Oncology Institution #
RTOG 1201
Case #

______ (Y/N) 19. Have you obtained the patient's consent for his or her tissue to be kept for use in research to learn about, prevent, treat, or cure cancer?

______ (Y/N) 20. Have you obtained the patient's consent for his or her blood to be kept for use in research to learn about, prevent, treat, or cure cancer?

______ (Y/N) 21. Have you obtained the patient's consent for his or her tissue to be kept for use in research about other health problems (for example: causes of diabetes, Alzheimer's disease, and heart disease)?

______ (Y/N) 22. Have you obtained the patient's consent for his or her blood to be kept for use in research about other health problems (for example: diabetes, Alzheimer's disease, or heart disease).

______ (Y/N) 23. Have you obtained the patient's consent to allow someone from this institution to contact him or her in the future to take part in more research?
ELIGIBILITY CHECKLIST - STEP 2 (6/25/13)

The following questions will be asked at Study Registration for STEP 2:

1. Institutional person randomizing case

2. Is the patient able to continue protocol treatment?
   If no, provide reason:
   1. Does not meet eligibility requirements, specify: ____________
   2. Physician preference,
   3. Patient refusal
   4. Other complicating disease
   5. Other, specify: ______________

3. Patient’s Initials (Last First Middle)

4. Verifying Physician

5. Patient ID

6. Calendar Base Date

7. Randomization Date

8. CA19-9 (1) < 1 or (2) ≥ 1 to ≤ 90 or (3) > 90

The Eligibility Checklist must be completed in its entirety prior to web registration. The completed, signed, and dated checklist used at study entry must be retained in the patient’s study file and will be evaluated during an institutional NCI/NRG Oncology audit.

Completed by ___________________________ Date ___________________________
1.0 INTRODUCTION (7/31/14)

1.1 The Efficacy of Radiation for Locally Advanced Pancreatic Cancer Is Uncertain

The LAP 07 trial evaluated the use of gemcitabine alone versus gemcitabine followed by radiation in patients with locally advanced pancreatic cancer (Hammel, 2013). In this trial, 442 patients were first randomized to gemcitabine alone or gemcitabine plus erlotinib for 4 months. Patients without progression (60%) were then randomized to 2 additional months of chemotherapy or chemoradiation. There was no improvement in survival with the addition of radiation following gemcitabine for patients with locally advanced pancreatic cancer. In contrast, a phase 3 trial by ECOG showed a survival advantage to the combination of radiotherapy and gemcitabine over gemcitabine alone (Loehrer 2011). The study was closed early because of slow accrual; however, in the 74 patients enrolled, median survival improved from 9.2 to 11.1 months (p=0.017). These results, together with the recent recognition that uncontrolled local growth is the cause of death in 30% of patients (Iacobuzio-Donahue et al., 2009) lend support to the notion that survival may be improved in selected patients with unresectable pancreatic cancer.

1.2 Rationale for Intensification of Radiation Therapy (10/9/14)

Previous attempts to escalate the radiation dose to pancreatic tumors, with or without chemotherapy, have been limited by severe toxicity. Intensity Modulated Radiation Therapy (IMRT) can reduce the dose to Organs-At-Risk and simultaneously allow an increase in target dose in this patient population (Spalding 2007). IMRT was used in a phase I/II trial (Ben-Josef 2012) at the University of Michigan, to escalate the dose from 50 to 60 Gy in 25 fractions delivered concurrently with full-dose gemcitabine (1000 mg/m² weekly on weeks 1, 2, 4, and 5 of radiotherapy). Dose limiting toxicity was defined as Grade ≥3 gastrointestinal toxicity, neutropenic fever/infection, or substantial deterioration (to Zubrod ≥3) of performance status, occurring between day 1 and 126. Of note, in this trial there was no elective lymph node irradiation and the Gross Tumor Volume (GTV) was expanded only by 0.5 cm to form the Clinical Target Volume (CTV). The trial accrued 50 patients and established that high-dose radiotherapy (55Gy in 25 fractions) can be delivered safely with concurrent full-dose gemcitabine, with the use of IMRT. The rate of severe toxicity (24%) observed at this dose compares favorably with toxicities reported with other contemporary regimens. There were also encouraging signals of efficacy. The median and 2-year survival in this trial (14.8 months and 30%, respectively) were significantly better than historical controls (11.2 months and 13%, respectively) (Murphy et al 2007). These results also compare favorably to other contemporary phase II and III trials in this patient population, with either 5-FU based- or gemcitabine-based platform. High-dose radiotherapy also improved the 2-year local control from 38% (historical controls, Murphy et al 2007) to 59%. Most importantly, 12 of 50 patients (24%) receiving high-dose radiotherapy were able to undergo resection with good outcomes; 10 patients (83%) had R0 resection and 5 patients (42%) had a major pathological response. The median survival in these patients was 32 months. The trial also confirmed that elective lymph node irradiation is not required in this setting and 0.5 cm GTV to CTV expansion is adequate. Investigators at Washington University also reported a favorable progression-free and overall survival (13.9 and 23.1 months, respectively) for 25 patients with locally advanced disease and 7 with borderline resectable disease following intensified radiation with 55 Gy in 25 fractions (Badiyan, 2014).

These trials demonstrate that intensification of local therapy with the use of high dose radiochemotherapy and highly conformal techniques can be delivered safely and results in encouraging local control rates and OS. Furthermore, it strongly suggests that survival can be extended in some patients with unresectable pancreatic cancer through improvement in local control and prevention or delay of local complications which can result in to death.

1.3 Rationale for Capecitabine and Radiation

Capecitabine is an oral fluoropyrimidine prodrug that is converted to 5-FU by thymidine phosphorylase at the site of the tumor. Capecitabine is similar in efficacy to 5FU plus leucovorin, as shown by a number of phase III trials (Hoff 2001, Twelves 2005, Van Cutsem 2001) and a meta-analysis of six large randomized phase III studies including 6171 patients with metastatic colorectal and gastric cancer (Cassidy 2008). The toxicity profile of capecitabine is more

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favorable compared with the bolus intravenous 5FU regimen (Hoff 2001, Twelves 2005, Van Cutsem 2001) and its use offers patients convenience, comfort and better quality of life. Capecitabine results in substantial savings in resource use compared to bolus 5-FU, a difference derived principally by the avoidance of hospital visits for intravenous drug administration, fewer treatment-related hospitalizations for toxicity, and less expensive drug therapy for the treatment of side-effects (Twelves 2001).

There is also strong rationale for the use of capecitabine as a radiosensitizer, an alternative to the concurrent use of intravenous 5-FU (Ben-Josef 2007, Liauw 2008). Capecitabine is commonly used as a radiosensitizer in the treatment of unresectable pancreatic cancer and has been used by RTOG previously (RTOG 0411). There is a significant amount of reported information regarding the safety of this regimen and robust efficacy data within RTOG. Dosimetric parameters for the duodenum using 63Gy in 28 fractions with concurrent capecitabine have recently been reported by investigators at MD Anderson Cancer Center (Kelly 2012).

1.4 Systemic Therapy With Gemcitabine + nab-Paclitaxel

A recent phase III study for patients with metastatic pancreatic cancer has demonstrated that the addition of nab-paclitaxel (Abraxane®) to gemcitabine demonstrated an improvement in survival as compared to gemcitabine alone. (Von Hoff, 2013) A total of 861 patients were randomly assigned to nab-paclitaxel plus gemcitabine (431 patients) or gemcitabine (430). The median overall survival was 8.5 months in the nab-paclitaxel–gemcitabine group as compared with 6.7 months in the gemcitabine group (hazard ratio for death, 0.72; 95% confidence interval [CI], 0.62 to 0.83; P<0.001). The survival rate was 35% in the nab-paclitaxel–gemcitabine group versus 22% in the gemcitabine group at 1 year, and 9% versus 4% at 2 years. The median progression-free survival was 5.5 months in the nab-paclitaxel–gemcitabine group, as compared with 3.7 months in the gemcitabine group (hazard ratio for disease progression or death, 0.69; 95% CI, 0.58 to 0.82; P<0.001); the response rate according to independent review was 23% versus 7% in the two groups (P<0.001). The most common adverse events of grade 3 or higher were neutropenia (38% in the nab-paclitaxel–gemcitabine group vs. 27% in the gemcitabine group), fatigue (17% vs. 7%), and neuropathy (17% vs. 1%). Febrile neutropenia occurred in 3% versus 1% of the patients in the two groups. In the nab-paclitaxel–gemcitabine group, neuropathy of grade 3 or higher improved to grade 1 or lower in a median of 29 days.

1.5 Rationale of Gemcitabine + nab-Paclitaxel Instead of FOLFIRINOX

Another option for systemic treatment of pancreatic cancer is the regimen of FOLFIRINOX (fluorouracil, oxaliplatin, leucovorin and irinotecan). In a phase III trial of FOLFIRINOX versus gemcitabine, the median overall survival was 11.1 months in the FOLFIRINOX group and 6.8 months in the gemcitabine group (hazard ratio for death, 0.57; 95% confidence interval [CI], 0.45 to 0.73; P<0.001). Therefore, FOLFIRINOX or gemcitabine plus nab-Paclitaxel each represent reasonable systemic regimens to investigate in locally advanced pancreatic cancer. FOLFIRINOX and gemcitabine + nab-Paclitaxel have not been directly compared. A recent analysis suggests that an important component of the differences reported in median survival between FOLFIRINOX and gemcitabine + nab-Paclitaxel may be due to patient selection (Peixoto 2014). Furthermore FOLFIRINOX may be associated with significant toxicities. For example, in a recent report at the 2014 American Society of Clinical Oncology GI Cancers Symposium, 75% of patients receiving FOLFIRINOX required dose adjustment, 30% had one or more dose delays, and one-third of patients developed grade III/IV toxicity (Metges 2014).

Given the toxicity profiles, we believe that gemcitabine with nab-Paclitaxel is a better handled ‘background chemotherapy’ regimen compared to FOLFIRINOX in good performance status patients prior to radiation treatment. Because gemcitabine and nab-Paclitaxel were continued until progression in the phase III trial by Von Hoff, they will be utilized until progression in all 3 arms in this trial for patients with locally advanced pancreatic cancer.
1.6 **SMAD4 Status as a Predictor of Pattern of Disease Progression and Mode-of-Death**

Recent data suggests that pancreatic cancers encompass distinct genetic subtypes with different patterns of failure and mode of death. In a rapid autopsy series, 30% of patients died of locally destructive pancreatic cancer, and 70% died with widespread metastatic disease (Iacobuzio-Donahue 2009). These distinct patterns of failure (locally destructive versus metastatic) were unrelated to clinical stage at presentation, treatment history, and histopathologic features. However, loss of SMAD4 immunolabeling was highly correlated with widespread metastasis while intact SMAD4 was highly correlated with a locally destructive phenotype.

We propose to develop cytology-determined SMAD4 status as a biomarker to guide therapy in future trials in unresectable pancreatic cancer. In particular, we would be interested to explore the concept of intensification of local therapy (high dose radiochemotherapy) or systemic therapy in patients with SMAD4 intact (i.e., locally destructive) and SMAD4 lost (i.e., widely metastatic), respectively.

The feasibility of determining SMAD4 status on diagnostic cytology specimens was tested recently at MD Anderson Cancer Center (Crane 2011) on a cohort of patients enrolled in a prospective phase II trial. Specimens were subjected to immunohistochemical staining and read by an expert pancreatic cancer cytopathologist. These results (see table below), albeit from a small sample size, are encouraging and document, in a prospective trial, the feasibility of testing for SMAD4 status on paraffin embedded cytology and that SMAD4 status correlates with pattern of disease progression.

<table>
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<th>Pattern of Progression, n=41</th>
<th>Locally destructive</th>
<th>Metastatic dominant</th>
<th>Unknown pattern</th>
<th>No progression</th>
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<tr>
<td>SMAD4 intact</td>
<td>11</td>
<td>4</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>SMAD4 loss</td>
<td>4</td>
<td>10</td>
<td>5</td>
<td>1</td>
</tr>
<tr>
<td>Chi square, $P=0.016$</td>
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We have investigated the robustness of the determination of SMAD4 status based on cytology in an independent patient cohort at Johns Hopkins. SMAD4 immunostaining of cytopathology and corresponding surgical specimens were performed in 20 patients. A total of 13/20 cases were concordant and 7/20 cases were discordant. Cytology identified correctly SMAD4 loss in 9/11 patients (82%) and SMAD4 intact in 5/9 patients (56%).

Based on these experiences we also estimate that approximately 30% of patients will not have sufficient material for immunostaining and that 10% of patients will have results that are equivocal. Thus approximately 40% of patients will have an undetermined SMAD4 status on cytology.

In the currently proposed study, we will retrospectively analyze the relationship between SMAD4 status as determined on cytology and the pattern of disease progression and mode of death. We will also conduct sub-group analyses to determine if standard or intensified radiochemotherapy improved survival in patients with SMAD4 intact status as compared to patients not receiving radiotherapy.

To ensure we have sufficient diagnostic material to conduct these analyses, it will be mandated that cell blocks (or core biopsies, where available) are sent to a central laboratory (Memorial Sloan-Kettering). SMAD4 status will be determined by immunohistochemistry and results will be used by NRG Oncology for stratification. Dr. Iacobuzio-Donahue will explore a number of other genetic methods for determining SMAD4 status in these specimens. These investigations will provide the data required to determine if SMAD4 status (cytology-based) could be used to drive treatment allocation in a future trial and if so, will provide a more robust assessment of this biomarker’s performance characteristics within the collaborative group setting.
Simultaneous with this trial we will optimize next generation sequencing analyses for SMAD4 genetic status using patient materials obtained from diagnostic cytology specimens. Specifically, we will use the already available Ampliseq panel that surveys all known cancer genes (including SMAD4) in association with the Ion Torrent sequencer to identify both intragenic mutations and homozygous deletions in these genes. The rationale for optimizing these analyses is twofold. First, it will allow us to correlate SMAD4 immunolabeling patterns with the genetic status of the same samples. This is important, as it will provide a validation of SMAD4 immunostaining patterns, and it will indicate if equivocal SMAD4 status is due to technical reasons versus an underlying biologic feature of SMAD4 regulation, i.e. altered degradation rates. Second, it is expected that next generation sequencing methods will become the mainstay of personalized medicine in general. Thus, this approach is not only highly novel but also timely in its approach.

1.7 Correlative Biological Studies (10/9/14)
Voluntary collection of additional tissue to be frozen and retained for molecular analysis will be requested. Ideally this will be a core biopsy of tumor that is snap frozen in liquid nitrogen and stored in a -80C freezer. If snap freezing in liquid nitrogen is not possible, freezing on dry ice before storage is also appropriate. These biopsies will be used at a later date to determine SMAD4 status using genetic methods (the gold standard). Specifically, frozen sections will be cut from the core biopsy and used for hematoxylin and eosin staining for histologic review and evaluation of sample quality (one section), followed by microdissection of neoplastic cells for extraction of gDNA. To preserve precious samples, an aliquot of genomic DNA (gDNA) will be whole genome amplified and only this gDNA used for PCR amplification and sequencing of the coding region of the SMAD4 gene (i.e., identification of intragenic mutations). Candidate mutations will be validated by an independent PCR and sequencing reaction of the original non-whole genome amplified (WGA) gDNA template to rule out artifacts related to this protocol. For those samples that are determined to be wild type for SMAD4, a separate serial section will also be used for fluorescent in situ hybridization (FISH) of the SMAD4 gene to evaluate for homozygous deletions. Overall, this strategy will not only allow identification of the mechanisms of SMAD4 loss (or retention) and their correlation to immunolabeling in this trial, but also the genetic status of the SMAD4 gene that correspond to equivocal staining in some cases. For example, we may find that cases with equivocal staining are predominantly wild type for the gene and this will be highly informative for understanding the outcome of patients treated in the equivocal staining group.

These biopsies will also prove valuable for evaluation of additional biomarkers of disease progression of interest to the group. For example, TP53 is also correlated with metastatic failure of pancreatic cancer in the absence of SMAD4 alterations. TP53 evaluations will entail methods similar to that described above for SMAD4. In addition, recent data has implicated loss of USP9x expression in pancreatic cancer as a marker of aggressive disease and metastatic failure. In this instance immunolabeling for USP9x will be performed on sections cut from the core biopsy.

Finally, we anticipate looking at tissue HENT1/ERCC1/ERCC2/TS/Topo-1/HuR/SPARC/RRM1 status and coding as well as possibly SNPs for their predictive value of benefit from gemcitabine and nab-Paclitaxel

We hypothesize that there will be a good correlation between genetic SMAD4 status and immunohistochemistry (IHC) on specimens; Patients with abnormal labeling patterns of Tp53 protein will have poor outcome; Patients with low expression of Usp9x will have poor outcome and there will be a good correlation between HENT1/ERCC1/ERCC2/TS/Topo-1/HuR/SPARC/RRM1 and response to gemcitabine and nab-Paclitaxel

When sufficient information is available from this study, a separate correlative science proposal detailing the scientific hypothesis, research plan, assay methods for use of biospecimens, and a complete statistical section will be submitted for review by the Cancer Therapy Evaluation Program (CTEP) in accordance with the NCI National Clinical Trials Network (NCTN) review policies for banked specimens.
1.8 **Summary of Rationale**
Following the LAP 07 trial, the role of chemoradiation, as compared to chemotherapy alone, in patients with locally advanced pancreatic cancer is uncertain. Preliminary data suggest that patients with SMAD4 intact status have a locoregional disease phenotype. This group may have the greatest potential benefit from a locoregional modality such as chemoradiation. We therefore will attempt to define a molecular subgroup of patients, such as those with SMAD4 intact status, who will benefit from chemoradiation. Based on the LAP07 trial, it is justified to use a non-radiation control arm. Based on the data from the University of Michigan we will also investigate an intensified radiation arm (63Gy) to maximize the potential to demonstrate a benefit from radiation - especially in patients who may have a locoregional disease phenotype such as SMAD4 intact status. More effective systemic control may also improve the likelihood that a benefit with radiation can be demonstrated. The gemcitabine + nab-Paclitaxel regimen was chosen as the systemic therapy for all three arms since the combination is superior to gemcitabine alone. Furthermore, gemcitabine + nab-Paclitaxel has a substantially lower rate of grade 3/4 toxicities and dose delays than FOLFIRINOX. Severe toxicity from the systemic chemotherapy regimen, such as FOLFIRINOX, could obscure the ability to define the impact of radiation on SMAD4 status.

2.0 **OBJECTIVES (7/31/14)**

2.1 **Primary Objectives**

2.1.1 To determine if intensified radiochemotherapy following gemcitabine and nab-Paclitaxel in patients with unresectable pancreatic cancer will show a signal for improved 2-year OS from 10% to 22.5% as compared to chemotherapy with gemcitabine and nab-Paclitaxel alone.

2.1.2 To determine if standard radiochemotherapy, following gemcitabine and nab-Paclitaxel, in patients with unresectable pancreatic cancer will show a signal for improved 2-year OS from 10% to 22.5% as compared to chemotherapy with gemcitabine and nab-Paclitaxel alone.

2.2 **Secondary Objectives**

2.2.1 To evaluate patterns of failure (local and systemic progression) by SMAD4 status and intensity of radiation therapy

2.2.2 To evaluate the impact of radiochemotherapy on OS for the subset of SMAD4 intact patients

2.2.3 To evaluate adverse events associated with the treatments.

2.2.4 To evaluate correlation between SMAD4 status determined by IHC and genetic SMAD4 status.

3.0 **PATIENT SELECTION (7/31/14)**

**NOTE: PER NCI GUIDELINES, EXCEPTIONS TO ELIGIBILITY ARE NOT PERMITTED.** For questions concerning eligibility, please contact the study data manager.

All conditions for Patient Eligibility and Patient Ineligibility must be met prior to Step 1 Registration.

3.1 **Conditions for Patient Eligibility (7/31/14)**

3.1.1 Histologically or cytologically proven diagnosis of adenocarcinoma of the pancreas prior to registration

3.1.2 Tumor diameter ≤ 7 cm

3.1.3 Unresectable by radiographic criteria (pancreas protocol CT or MRI) or exploration within 30 days prior to registration. (See Appendix IV and Appendix V for details)

3.1.4 A cell block or core biopsy must be submitted for central review and analysis of SMAD4 status as soon as possible following step 1 registration (see Section 10.2 for details of tissue submission)

3.1.5 No distant metastases, based upon the following minimum diagnostic workup:

- History/physical examination within 30 days prior to registration
- Whole body FDG-PET/CT within 30 days prior to registration

**NOTE:** If whole-body FDG-PET/CT is not performed, CT of the chest and CT (or MRI) of abdomen and pelvis must be obtained (imaging of abdomen and pelvis need not be repeated if already included in pancreas protocol study)
3.1.6  Zubrod Performance Status 0-1 within 30 days prior to registration
3.1.7  Age ≥ 18;
3.1.8  CBC/differential obtained within 14 days prior to step 1 registration, with adequate bone marrow function defined as follows:
   - Absolute neutrophil count (ANC) ≥ 1,500 cells/mm³
   - Platelets ≥ 100,000 cells/mm³
   - Hemoglobin ≥ 8.0 g/dl (NOTE: The use of transfusion or other intervention to achieve Hgb ≥ 8.0 g/dl is acceptable)
3.1.9  Additional laboratory studies within 14 days prior to registration:
   - CA19-9  NOTE: in the event that a stent has been placed and biliary obstruction has been relieved, the CA19-9 should be drawn post stent placement
   - Creatinine < 2 mg/dl; GFR > 50 mL/min (Cockroft and Gault formula)
   - Bilirubin < 1.5 x ULN
   - ALT and AST ≤ 2.5 x ULN
   - aPT T, PT ≤1.2 x ULN
3.1.10 Patient must provide study specific informed consent prior to study entry
3.1.11 Women of childbearing potential and male participants must practice adequate contraception during protocol treatment and for at least 6 months following treatment
3.1.12 For females of child-bearing potential, negative serum pregnancy test within 30 days prior to registration

3.2  Conditions for Patient Ineligibility (10/9/14)
3.2.1  More than one primary lesion
3.2.2  Prior invasive malignancy (unless disease free for a minimum of 1095 days [3 years]); Non-melanomatous skin cancer and previous early prostate cancer that had a non-rising PSA are eligible
3.2.3  Prior systemic anti-cancer therapy for pancreatic cancer; note that prior chemotherapy for a different cancer is allowable
3.2.4  Prior radiation therapy to the abdomen that would result in overlap of radiation therapy fields
3.2.5  Severe, active co-morbidity, defined as follows:
   - Unstable angina and/or congestive heart failure requiring hospitalization within the last 6 months
   - Transmural myocardial infarction within the last 6 months
   - Acute bacterial or fungal infection requiring intravenous antibiotics at the time of registration
   - Chronic Obstructive Pulmonary Disease exacerbation or other respiratory illness requiring hospitalization or precluding study therapy within 30 days before registration
   - Hepatic insufficiency resulting in clinical jaundice and/or coagulation defects; note, however, that laboratory tests for liver function (except as outlined in Section 3.1) and coagulation parameters are not required for entry into this protocol
   - Acquired Immune Deficiency Syndrome (AIDS) based upon current Centers for Disease Control (CDC) definition; note, however, that HIV testing is not required for entry into this protocol. The need to exclude patients with AIDS from this protocol is necessary because the treatments involved in this protocol may be significantly immunosuppressive. Protocol-specific requirements may also exclude immunocompromised patients
3.2.6  Pregnancy or women of childbearing potential, women who cannot discontinue breastfeeding and men who are sexually active and not willing/able to use medically acceptable forms of contraception; this exclusion is necessary because the treatment involved in this study may be significantly teratogenic
3.2.7  Prior allergic reaction to the study drug(s) involved in this protocol
3.2.8  Pre-existing Grade 2 or greater neuropathy
3.2.9  Distant metastases
4.0 PRETREATMENT EVALUATIONS/ MANAGEMENT
NOTE: This section lists baseline evaluations needed before the initiation of protocol treatment that do not affect eligibility.

4.1 Required Evaluations/Management (7/31/14)
4.1.1 Biliary obstruction must be relieved prior to initiation of protocol therapy, preferably with an endobiliary metal wall stent. Plastic stents are much more prone to occlusion. If a patient presents with a plastic stent, it is highly recommended it be replaced with a metal stent prior to initiation of protocol therapy. If a gastric or biliary bypass has been performed, it must be performed at least 28 days prior to step 1 registration and patient must have recovered from procedure.

4.1.2 Albumin and electrolytes—Na, K, Cl, Mg, CO2 within 14 days prior to step 1 registration

4.2 Highly Recommended Evaluations/Management
Note that these evaluations/interventions are highly recommended as part of good clinical care of patients on this trial but are not required.

4.2.1 It is recommended strongly that patients be put on a proton pump inhibitor or other effective antacid therapy during protocol therapy. See Section 9.1 for a list of permitted medications.

4.2.2 Careful attention should be paid to the patient’s nutritional status; See Section 9.1 for a list of permitted food supplements and appetite stimulants.

4.2.3 Pain interferes with the ability to deliver effective therapy and should be managed aggressively; See Section 9.1.

5.0 REGISTRATION PROCEDURES (9/23/13)
Access requirements for OPEN, Medidata Rave, and TRIAD:
Site staff will need to be registered with CTEP and have a valid and active CTEP Identity and Access Management (IAM) account. This is the same account (user id and password) used for the CTSU members’ web site. To obtain an active CTEP-IAM account, go to https://eapps-ctep.nci.nih.gov/iam.

5.1 Pre-Registration Requirements for IMRT Treatment Approach (7/31/14)
5.1.1 In order to utilize IMRT on this study, the institution must have met specific technology requirements and have provided baseline physics information. Instructions for completing these requirements or determining if they already have been met are available on the Imaging and Radiation Oncology Core (IROC) Houston web site. Visit http://irochouston.mdanderson.org and select “Credentialing” and “Credentialing Status Inquiry”.

An IMRT phantom study with IROC Houston must be successfully completed (if the institution has not previously met this IMRT credentialing requirement). Instructions for requesting and irradiating the phantom are available on the IROC Houston web site at http://irochouston.mdanderson.org; select “Credentialing” and “RTOG”. Upon review and successful completion of the phantom irradiation, IROC Houston will notify both the registering institution and IROC Philadelphia that the institution has completed this requirement. Subsequently, IROC Philadelphia will notify the institution that IMRT credentialing requirement has been met.

5.1.2 The institution or investigator must update or complete a new IMRT Facility Questionnaire (available on the IROC Houston web site at http://irochouston.mdanderson.org) and send it to RTOG for review prior to entering any cases. RTOG Headquarters will notify the institution when all requirements have been met and the institution is RT credentialed to enter patients onto this study.

5.2 Digital RT Data Submission to RTOG Using TRIAD (7/31/14)
TRIAD, the American College of Radiology’s (ACR) image exchange application, will be used for dosimetry digital treatment data.

TRIAD Access Requirements:
• Site physics staff who will submit images through TRIAD will need to be registered with The Cancer Therapy Evaluation Program (CTEP) and have a valid and active CTEP Identity and Access Management (IAM) account. Please refer to Section 5.0 of the protocol for instructions on how to request a CTEP-IAM account.

• To submit images, the site physics user must have been assigned the 'TRIAD site user' role on the relevant Group or CTSU roster. Users should contact your site Lead RA to be added to your site roster. Users from other cooperative groups should follow their procedures for assignment of roster roles.

• RAs are able to submit standard of care imaging through the same method.

**TRIAD Installations:**

When a user applies for a CTEP-IAM account with proper user role, he/she will need to have the TRIAD application installed on his/her workstation to be able to submit images. TRIAD installation documentation can be found on the NRG Oncology/RTOG website Core lab tab.

This process can be done in parallel to obtaining your CTEP-IAM account username and password.

If you have any questions regarding this information, please send an e-mail to the TRIAD Support mailbox at TRIAD-Support@acr.org.

5.3 **Regulatory Pre-Registration Requirements (7/31/14)**

5.3.1 This study is supported by the NCI Cancer Trials Support Unit (CTSU) Regulatory Office and OPEN.

Prior to the recruitment of a patient for this study, investigators must be registered members of a lead protocol organization. Each investigator must have an NCI investigator number and must maintain an "active" investigator registration status through the annual submission of a complete investigator registration packet (FDA Form 1572 with original signature, current CV, Supplemental Investigator Data Form with signature, and Financial Disclosure Form with original signature) to the Pharmaceutical Management Branch (PMB), CTEP, DCTD, NCI. These forms are available on the CTSU registered member web site http://ctep.cancer.gov/investigatorResources/investigator_registration.htm. For questions, please contact the CTEP Investigator Registration Help Desk by e-mail at pmbregpend@ctep.nci.nih.gov.

The Cancer Therapy Evaluation Program (CTEP) Identity and Access Management (IAM) application is a web-based application intended for use by both Investigators (i.e., all physicians involved in the conduct of NCI-sponsored clinical trials) and Associates (i.e., all staff involved in the conduct of NCI-sponsored clinical trials). Associates will use the CTEP-IAM application to register (both initial registration and annual re-registration) with CTEP and to obtain a user account. Investigators will use the CTEP-IAM application to obtain a user account only. (See CTEP Investigator Registration Procedures above for information on registering with CTEP as an Investigator, which must be completed before a CTEP-IAM account can be requested.) An active CTEP-IAM user account will be needed to access all CTEP and CTSU (Cancer Trials Support Unit) websites and applications, including the CTSU members' web site. Additional information can be found on the CTEP web site at http://ctep.cancer.gov/branches/pmb/associate_registration.htm. For questions, please contact the CTEP Associate Registration Help Desk by e-mail at ctepreghelp@ctep.nci.nih.gov.

Each investigator or group of investigators at a clinical site must obtain IRB approval for this protocol and submit IRB approval and supporting documentation to the CTSU Regulatory Office before they can enroll patients. Study centers can check the status of their registration packets by
querying the Regulatory Support System (RSS) site registration status page of the CTSU member web site by entering credentials at https://www.ctsu.org.

Requirements for RTOG 1201 site registration:
- CTSU IRB Certification
- CTSU IRB/Regulatory Approval Transmittal Sheet
- CTSU RT Facilities Inventory Form (if applicable)
- IRB approval letter IRB/REB approved consent (English language versions)
- IRB/REB assurance number renewal information, as appropriate

Submit completed forms along with a copy of your IRB Approval and Informed Consent to the CTSU Regulatory Office, where they will be entered and tracked in the CTSU RSS.

CTSU Regulatory Office
1818 Market Street, Suite 1100
Philadelphia, PA 19103
Phone: 1-866-651-2878
Fax: 215-569-0206
E-mail: CTSURegulatory@ctsu.coccg.org (for regulatory document submission only)

Check the status of your site’s registration packets by querying the RSS site registration status page of the members' section of the CTSU web site. (Note: Sites will not receive formal notification of regulatory approval from the CTSU Regulatory Office.)

- Go to https://www.ctsu.org and log in to the members’ area using your CTEP-IAM username and password
- Click on the Regulatory tab at the top of your screen
- Click on the Site Registration tab
- Enter your 5-character CTEP Institution Code and click on Go

5.4 Summary of Patient Registration Procedures (7/31/14)

Once the site has met pre-registration requirements, this study incorporates a 2-step registration process:

**Step 1** of registration entails OPEN registration as detailed below, at which time the patient will be assigned to gemcitabine + nab-Paclitaxel.

**Step 2** of registration requires a second web registration for all patients, at which time the patient will be randomized to Arm 1, 2, or 3. **Note:** If a patient is not going on to randomization (e.g. due to progression, step 2 registration must still be completed via web registration.

5.5 Registration (7/31/14)

5.5.1 OPEN Registration Instructions

Patient registration can occur only after evaluation for eligibility is complete, eligibility criteria have been met, and the study site is listed as ‘approved’ in the CTSU RSS. Patients must have signed and dated all applicable consents and authorization forms.

Patient enrollment will be facilitated using the Oncology Patient Enrollment Network (OPEN). OPEN is a web-based registration system available on a 24/7 basis. All site staff will use OPEN to enroll patients to this study. It is integrated with the CTSU Enterprise System for regulatory and roster data and, upon enrollment, initializes the patient position in the Rave database. OPEN can be accessed at https://open.ctsu.org or from the OPEN tab on the CTSU members' web site https://www.ctsu.org.

Prior to accessing OPEN site staff should verify the following:
- All eligibility criteria have been met within the protocol stated timeframes. Site staff should use the registration forms provided on the group or CTSU web site as a tool to verify eligibility.
- All patients have signed an appropriate consent form and HIPPA authorization form (if applicable).

Access requirements for OPEN:
- See Section 5.0 for obtaining a CTEP-IAM account. To perform registrations, the site user must have been assigned the 'Registrar' role on the relevant Group or CTSU roster.
- To perform registrations on protocols for which you are a member of NRG Oncology, you must have an equivalent 'Registrar' role on the NRG Oncology roster. Role assignments are handled through the Groups in which you are a member.
- To perform registrations to trials accessed via the CTSU mechanism (i.e., non-Lead Group registrations) you must have the role of Registrar on the CTSU roster. Site and/or Data Administrators can manage CTSU roster roles via the new Site Roles maintenance feature under RSS on the CTSU members' web site. This will allow them to assign staff the "Registrar" role.

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

Further instructional information is provided on the CTSU members' web site OPEN tab or within the OPEN URL. For any additional questions contact the CTSU Help Desk at 1-888-823-5923 or ctsucontact@westat.com

In the event that the OPEN system is not accessible, participating sites can contact web support for assistance with web registration: websupport@acr.org or call the Registration Desk at (215) 574-3191, Monday through Friday, 8:30 a.m. to 5:00 p.m. ET. The registrar will ask the site to fax in the eligibility checklist and will need the registering individual’s e-mail address and/or return fax number. This information is required to assure that mechanisms usually triggered by the OPEN web registration system (e.g. drug shipment and confirmation of registration) will occur.

6.0 RADIATION THERAPY (7/31/14)

NOTE: This trial is utilizing TRIAD for dosimetry digital treatment data submission. See Section 5.2 for information on installing TRIAD for submission of digital RT data prior to enrolling patients.

NOTE: Intensity Modulated RT (IMRT) credentialing is mandatory. IMRT is required in Arm 1; 3D-CRT or IMRT are allowed in Arm 2. All cases must have the treatment plan and pancreatic protocol CT (see Appendix IV) submitted 2 weeks prior to RT treatment. All Arm1 IMRT cases require a pre-treatment review prior to delivery of radiation treatment. 3 business days are required to complete the pre-treatment review. This review is aimed at providing feedback from the study Principal Investigators on the institution’s contours and treatment plan.

NOTE: Concurrent Treatment (Radiation/Capecitabine) must start 3-5 weeks after the last dose of administration of chemotherapy.

6.1 Dose Specifications (7/31/14)

The dose to the planning target volume (PTV) will be:
- Arm 1: 63 Gy in 2.25 Gy per fraction in 28 fractions delivered 5 days a week. Plans must be normalized such that ninety-five percent of the PTV receives 95% of the prescribed dose. The maximum dose (MAX Dose) allowed (for a Per Protocol score) within the PTV to a point that is 0.03 cc is 110% of the prescribed dose. The minimum dose (MIN Dose) in the PTV for a point that is 0.03 cc is 85% of the prescribed dose.
- Arm 2: 50.4 Gy in 1.8 Gy per fraction in 28 fractions delivered 5 days a week. Plans must be normalized such that ninety-five percent of the PTV must receive
at least 97% of the dose. The MAX Dose allowed (for a Per Protocol score) within the PTV to a point that is 0.03 cc is 105% of the prescribed dose.

6.2 Technical Factors (7/31/14)
6.2.1 Photon beams of 6MV or higher should be used.
6.2.2 For IMRT in Arm 1 and Arm 2 the following beam arrangement is recommended and should be used as a default starting point. This arrangement results in optimal dose distribution in the majority of patients.

<table>
<thead>
<tr>
<th>Couch Angle</th>
<th>Gantry Angle</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
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<tr>
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<td>90</td>
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</tr>
<tr>
<td>90</td>
<td>330</td>
</tr>
</tbody>
</table>

6.2.3 For 3D planning in Arm 2, a 3-field (Right and left laterals and an AP) should be the default beam arrangement. Other arrangements are acceptable if they provide dosimetric advantages.

6.3 Localization, Simulation, and Immobilization
6.3.1 Treatment planning will be based on a helical pancreatic protocol CT (see Appendix IV) obtained in the treatment position following administration of oral (VoLumen or water is recommended) and intravenous contrast. Simulation scan slice thickness must be no greater than 2.5 mm, and the contouring can be done every other slice with interpolation if desired. These images must be uploaded in TRIAD for Rapid Review as part of the QA process no later than 2 weeks prior to the start of treatment (see Section 12.2).

6.3.2 Patients will be simulated (and treated) supine with arms up. Immobilization is required. A thorax board is recommended. Two leveling marks on each side of the patient (2 on the right and 2 on the left) are required.

6.3.3 The isocenter should be imaged daily prior to treatment. The patient should be aligned to the vertebral bodies adjacent to the PTV. Localization (port) films must be taken for each treatment field once a week and made available for review if required.

6.4 Treatment Planning/Target Volumes (7/31/14)
6.4.1 Arm 1
- The gross tumor volume (GTV) will be the primary tumor plus any involved regional lymph nodes identifiable on CT/MRI (≥1.0 cm) or on PET scan
- The clinical target volume (CTV) will be defined as the GTV plus 0.5 cm
- The planning target volumes (PTV) will be the CTV plus 0.5 cm

6.4.2 Arm 2
- The gross tumor volume (GTV) will be the primary tumor plus any involved regional lymph nodes identifiable on CT/MRI (≥1.0 cm) or on PET scan
- The clinical target volume (CTV) will be defined as the GTV plus 1.5 cm
- The planning target volumes (PTV) will be the CTV plus 0.5 cm in all directions when breath-hold, gating or tracking techniques are used. With free breathing, it is recommended that CTV to PTV expansion in the cranio-caudal direction will be based on target motion as assessed by 4D CT scan. Cranio-caudal expansion should be in the range of 0.5 -1.5 cm). Expansions in all other directions will be 0.5 cm

6.4.3 Breathing motion management
In Arm 1, for patients with head or tail of pancreas tumors, only the following motion management methods are allowed:
• Breath-hold (with the use of Active Breathing Control [ABC], SDX, or similar devices)
• Self-held breathing with respiratory monitoring (e.g. RPM) as a beam-hold mechanism.
• Fluoroscopic/electromagnetic gating or tracking using implanted fiducial markers in the tumor.

Gating or tracking based on diaphragmatic or abdominal wall excursion, without additional confirmation by an appropriate fiducial maker(s) is not allowed.

**NOTE:** Free breathing treatment is allowed in Arm 1 only for patients with neck and body tumors with vascular encasement, with 4D scan showing ≤ 5mm motion. EUS guided placement of fiducial markers is highly recommended. If free breathing treatment is planned, the CTV to PTV expansion should be based on 4D scan assessment of target motion and not greater than 1.0 cm.

For Arm 2 (standard dose radiotherapy) all of the above are permitted but not required. Free breathing is allowed. It is highly recommended to study target motion with a 4D CT scan and expand CTV to PTV based on that study.

For any breathing management method, pre-treatment image guidance to an appropriate anatomic surrogate is required on each fraction. Appropriate surrogates include the vertebral bodies adjacent to the PTV for breath-hold treatments, or implanted fiducials for tracked treatments. If in-room IGRT is used, soft tissue may be selected but caution is advised as the visibility of the pancreas on non-enhanced in-room volumetric imaging may be very limited. 2D IGRT techniques should not be used for soft-tissue matching.

### 6.5 Critical Structures (7/31/14)

**NOTE:** All required structures marked as “required” in the tables below must be labeled as for digital RT data submission. The use of underscores and capital letters as indicated is essential. Resubmission of data may be required if labeling of structures does not conform to the standard dicom name listed.

### Arm 1

<table>
<thead>
<tr>
<th><strong>Standard Name</strong></th>
<th><strong>Description</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>PTV_6300</td>
<td>PTV to receive 63 Gy Required</td>
</tr>
<tr>
<td>CTV_6300</td>
<td>CTV to receive 63 Gy Required</td>
</tr>
<tr>
<td>GTV_6300</td>
<td>GTV to receive 63 Gy Required</td>
</tr>
<tr>
<td>Liver</td>
<td>Liver Required</td>
</tr>
<tr>
<td>Stomach</td>
<td>Stomach Required</td>
</tr>
<tr>
<td>Duodenum</td>
<td>Duodenum Required</td>
</tr>
<tr>
<td>SmallBowel</td>
<td>Small Bowel Required</td>
</tr>
<tr>
<td>SpinalCord</td>
<td>Spinal Cord Required</td>
</tr>
<tr>
<td>Kidney_R</td>
<td>Right Kidney Required</td>
</tr>
<tr>
<td>Kidney_L</td>
<td>Left Kidney Required</td>
</tr>
</tbody>
</table>
Arm 2

<table>
<thead>
<tr>
<th>Standard Name</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>PTV_5040</td>
<td>PTV to receive 50.4 Gy</td>
</tr>
<tr>
<td>CTV_5040</td>
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</tr>
<tr>
<td>GTV_5040</td>
<td>GTV to receive 50.4 Gy</td>
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<td>Liver</td>
</tr>
<tr>
<td>Stomach</td>
<td>Stomach</td>
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<tr>
<td>Duodenum</td>
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<tr>
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<td>Small Bowel</td>
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<tr>
<td>SpinalCord</td>
<td>Spinal Cord</td>
</tr>
<tr>
<td>Kidney_R</td>
<td>Right Kidney</td>
</tr>
<tr>
<td>Kidney_L</td>
<td>Left Kidney</td>
</tr>
</tbody>
</table>

6.5.1 Normal Structures

The normal structures to be contoured are: left and right kidneys, liver, stomach, duodenum, small intestine, spinal cord. If the duodenum is invaded by the tumor, the normal duodenum outside of this region should be contoured as the critical structure.

6.5.2 Normal-tissue dose-volume constraints

For IMRT in Arm 1

<table>
<thead>
<tr>
<th>Structure</th>
<th>Constraints</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kidney_L</td>
<td>90% of the volume equivalent to one kidney ≤ 18Gy; This volume can be, for instance 30% of one kidney plus 70% of the second kidney</td>
</tr>
<tr>
<td>Kidney_R</td>
<td>90% of the volume equivalent to one kidney ≤ 18Gy; This volume can be, for instance 30% of one kidney plus 70% of the second kidney</td>
</tr>
<tr>
<td>Liver</td>
<td>Mean dose ≤ 28 Gy</td>
</tr>
<tr>
<td>SmallBowel</td>
<td>Max Dose to a small point of 0.03 cc must be ≤ 58Gy.</td>
</tr>
<tr>
<td></td>
<td>V50&lt;10cc</td>
</tr>
<tr>
<td></td>
<td>V45&lt;135cc</td>
</tr>
<tr>
<td>Stomach</td>
<td>Max dose to a small point of 0.03 cc ≤ 58Gy.</td>
</tr>
<tr>
<td></td>
<td>V50&lt;5cc</td>
</tr>
<tr>
<td></td>
<td>V45&lt;75cc</td>
</tr>
<tr>
<td>SpinalCord</td>
<td>Max dose ≤ 45Gy</td>
</tr>
<tr>
<td>Duodenum</td>
<td>Max dose to a small point of 0.03 cc ≤ 59Gy.</td>
</tr>
<tr>
<td></td>
<td>V56&lt;5cc</td>
</tr>
<tr>
<td></td>
<td>V45&lt;30cc</td>
</tr>
</tbody>
</table>
For IMRT or 3DCRT in Arm 2

<table>
<thead>
<tr>
<th>Structure</th>
<th>Constraints</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kidney_L</td>
<td>90% of the equivalent volume of one kidney ≤ 18 Gy;</td>
</tr>
<tr>
<td>Kidney_R</td>
<td>This volume can be for instance 30% of one kidney plus 70% of the second kidney</td>
</tr>
<tr>
<td>SmallBowel</td>
<td>Max dose &lt; 51 Gy</td>
</tr>
<tr>
<td>Stomach</td>
<td>Max dose &lt; 51 Gy</td>
</tr>
<tr>
<td>Duodenum</td>
<td>Max dose &lt; 51 Gy</td>
</tr>
<tr>
<td>Liver</td>
<td>Mean dose ≤ 28 Gy</td>
</tr>
<tr>
<td>SpinalCord</td>
<td>Max dose ≤ 45 Gy</td>
</tr>
</tbody>
</table>

6.6 Documentation Requirements (10/9/14)

6.6.1 Quality Assurance Documentation
The following must be uploaded to TRIAD:
- A pancreas protocol CT scan (multi-detector CT scans, slice thickness < 2.5 mm contrast-enhanced using a bi-phasic technique; see Appendix IV) and/or MRI showing the extent of the tumor
- The CT-simulation images along with target and critical structure contours and the treatment plan must be digitally uploaded to TRIAD (See Section 12.2). The imaging and dosimetry plans will be reviewed prior to the start of treatment by the Principal Investigator, Edgar Ben-Josef, MD or the Radiation Oncology Co-Chairs, Christopher Crane, MD and Joseph Herman, MD. In order to complete this Rapid Review process, the required information must be received at IROC Philadelphia at least 2 weeks before the start of radiation treatment. The treatment plan must be approved PRIOR TO DELIVERY of therapy

6.7 Compliance Criteria (7/31/14)
The pre-treatment review process for this protocol is aimed at avoiding incorrect contouring of target and OARs for this protocol and ensuring that dose-volume goals and constraints are met.

6.7.1 Dose and Volumes
Per Protocol: As required in Section 6.1 and Section 6.5

Variation Acceptable:
- For IMRT plans in Arm 1:
  - Minimum dose (MIN Dose) to a point that is 0.03 cc in the PTV can fall below 85% of the prescribed but not below 80% of this dose
  - Maximum dose (MAX Dose) in the PTV goes above 110% but does not exceed 115% of prescribed dose
- For 3D-CRT and IMRT plans in Arm 2:
  - Maximum dose within the PTV goes above than 105% of the prescribed dose, but does not exceed 110% of this dose

Deviation Unacceptable:
Any doses that do not meet the limits for Per Protocol or Variation Acceptable will be scored as Deviation Unacceptable

6.7.2 Radiotherapy interruptions should be clearly documented in the patient’s medical record
Per Protocol: 0-7 days
Variation Acceptable: 8-14 days
6.7.3 **Compliance Criteria for Critical Structures**

The compliance criteria for the critical structures identified for this protocol are based on the planning constraints presented in Section 6.5.

**Kidneys:**
- Per protocol: the requirements in Section 6.5 are fulfilled
- Variation Acceptable: 80% of equivalent volume of one kidney receives $\leq 18$ Gy and 20% receives a higher dose
- Deviation Unacceptable: Dose limits for Variation Acceptable are exceeded

**Spinal cord:**
- Per protocol: the requirements in Section 6.5 are fulfilled
- Variation Acceptable: None
- Deviation Unacceptable: Dose limits for Per Protocol are exceeded

**Liver:**
- Per protocol: the requirements in Section 6.5 are fulfilled
- Variation Acceptable: Mean liver dose exceeds 28 Gy but is $\leq 30$ Gy
- Deviation Unacceptable: The dose limit for Variation Acceptable is exceeded

**Duodenum:**
- Per protocol: the requirements in Section 6.5 are fulfilled
- Variation Acceptable: Max is $> 59$ Gy but dose $\leq 61$ Gy
- Deviation Unacceptable: Max dose $> 61$ Gy

**Small bowel and stomach**
- Per protocol: the requirements in Section 6.5 are fulfilled
- Variation Acceptable: Max dose is $> 58$ Gy but $\leq 60$ Gy
- Deviation Unacceptable: Max dose $> 60$ Gy

<table>
<thead>
<tr>
<th>Structure</th>
<th>Per Protocol</th>
<th>Variation Acceptable*</th>
</tr>
</thead>
<tbody>
<tr>
<td>PTV – ARM 1 IMRT</td>
<td>Prescribed dose 63Gy</td>
<td>95% of the PTV must receive 95% of prescribed dose</td>
</tr>
<tr>
<td></td>
<td></td>
<td>MAX Dose to a point that is 0.03 cc must be $\leq 110%$ of prescribed dose</td>
</tr>
<tr>
<td></td>
<td></td>
<td>MIN Dose to a point that is 0.03 cc must be $\geq 85%$ of the prescribed dose</td>
</tr>
<tr>
<td>PTV – ARM 2 3DCRT and IMRT</td>
<td>Prescribed dose 50.4Gy</td>
<td>95% of the PTV must receive $\geq 97%$ of prescribed dose</td>
</tr>
<tr>
<td></td>
<td></td>
<td>MAX Dose to a point that is 0.03 cc must be $\leq 105%$ of prescribed dose</td>
</tr>
<tr>
<td>Kidney_L Kidney_R</td>
<td>90% of volume of the equivalent of one kidney</td>
<td>80% of the volume of the equivalent of one kidney receives $\leq 18$ Gy</td>
</tr>
</tbody>
</table>
receives a dose that is < 18Gy

<table>
<thead>
<tr>
<th>Tissue</th>
<th>MAX Dose to a point that is 0.03 cc is ≤ 45 Gy</th>
<th>No variation allowed</th>
</tr>
</thead>
<tbody>
<tr>
<td>Liver</td>
<td>MEAN Dose ≤28 Gy</td>
<td>MEAN Dose ≤30 Gy</td>
</tr>
<tr>
<td>Small Bowel, Stomach, Duodenum</td>
<td>Max Dose to a small point of 0.03 cc must be ≤58Gy</td>
<td>Max dose is &gt; 58 Gy but ≤ 60 Gy</td>
</tr>
<tr>
<td>ARM 1 IMRT Prescribed dose 63Gy</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Duodenum ARM 1 IMRT Prescribed dose 63Gy PTV</td>
<td>Max dose to a small point of 0.03 cc ≤ 59Gy</td>
<td>Max dose is &gt;59 Gy but ≤ 61 Gy</td>
</tr>
<tr>
<td>Small Bowel, Stomach, Duodenum ARM 2 3DCRT and IMRT Prescribed dose 50.4Gy</td>
<td>Max dose ≤51 Gy</td>
<td>Max dose &gt;51 Gy but ≤53 Gy</td>
</tr>
</tbody>
</table>

**NOTE:** Any doses that do not meet either the Per Protocol or Variation Acceptable dose limits are will be scored as Deviation Unacceptable.

### 6.8 R.T. Quality Assurance Reviews (7/31/14)

#### 6.8.1 Pre-treatment Review

For high-dose IMRT patients (Arm 1), the imaging and dosimetry plans must be reviewed and approved prior to the start of treatment by the Principal Investigator Dr. Ben-Josef or the Radiation Oncology Co-Chairs Dr. Crane or Dr. Herman.

#### 6.8.2 Final Review

The Radiation Oncology Chair Edgar Ben Josef, MD and the Radiation Oncology Co-Chairs, Christopher Crane MD and Joseph Herman, MD will also perform a review of the cases not undergoing a pre-treatment review on an ongoing basis once complete data has been received at IROC Philadelphia. The final cases will be reviewed within 3 months after this study has reached the target accrual or as soon as complete data for all cases enrolled has been received at IROC Philadelphia, whichever occurs first.

### 6.9 Radiation Therapy Adverse Events

Adverse effects related to radiation therapy include nausea/vomiting, diarrhea, weight loss, fatigue, myelosuppression, skin erythema, gastric or duodenal ulcer, gastrointestinal bleeding or perforation, intestinal obstruction, fistulae, subcutaneous fibrosis, esophagitis, and esophageal stricture.

### 6.10 Radiation Therapy Adverse Event Reporting

See Section 7.12 for AE reporting guidelines

### 7.0 DRUG THERAPY (7/31/14)

Protocol treatment (chemotherapy) must begin within 14 days after step 1 registration.

#### 7.1 Step 1: Chemotherapy with gemcitabine + nab-Paclitaxel (All patients) (7/31/14)

<table>
<thead>
<tr>
<th>DRUG</th>
<th>DOSE</th>
<th>DURATION</th>
</tr>
</thead>
<tbody>
<tr>
<td>nab-Paclitaxel</td>
<td>125 mg/m² weekly, three on/one off for 3 cycles</td>
<td>As a 30-40 minute infusion</td>
</tr>
<tr>
<td>Gemcitabine</td>
<td>1000 mg/m² weekly, three on/one off for 3 cycles</td>
<td>Over 30 minutes after nab-Paclitaxel infusion</td>
</tr>
</tbody>
</table>

**NOTE:** 1 Cycle =4 weeks: 3 weeks of drug with 1 week off.

All patients will receive 3 cycles of treatment then undergo a restaging CT scan to be performed after completion of day 15 chemotherapy of cycle 3 and before cycle 4.
7.2  Step 2 Randomization: Chemotherapy with gemcitabine + nab-Paclitaxel (for non-progressing patients) (7/31/14)

Patients cannot proceed to randomization chemotherapy if one or both drugs must be stopped permanently or if > 2 dose reductions have occurred prior to randomization.

**NOTE:** The first cycle of step 2 treatment will begin immediately following the off week of cycle 3 step 1 treatment.

Patients without disease progression will be randomized to either one of the arms described below:

<table>
<thead>
<tr>
<th>ARM 1</th>
<th>ARM 2</th>
<th>ARM 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gemcitabine, 1000 mg/m² weekly and nab-Paclitaxel, 125 mg/m² weekly (three on/one off) for 4 weeks</td>
<td>Gemcitabine, 1000 mg/m² weekly and nab-Paclitaxel, 125 mg/m² weekly (three on/one off) for 4 weeks</td>
<td>Gemcitabine, 1000 mg/m² weekly and nab-Paclitaxel, 125 mg/m² weekly (three on/one off) until progression</td>
</tr>
<tr>
<td>One cycle only of Gemcitabine + nab-Paclitaxel 3-5 weeks post last chemotherapy administration. This is followed by concurrent Capecitabine* and RT 2-6 weeks after completion of radiation: Gemcitabine + nab-paclitaxel until progression.</td>
<td>One cycle only of Gemcitabine + nab-Paclitaxel 3-5 weeks post last chemotherapy administration. This is followed by concurrent Capecitabine* and RT 2-6 weeks after completion of radiation: Gemcitabine + nab-paclitaxel until progression.</td>
<td>No chemoradiation.</td>
</tr>
</tbody>
</table>

7.3  Concurrent Treatment (Capecitabine and Radiation)- Arms 1 and 2 ONLY (10/9/14)

*Capecitabine:
Capecitabine 825 mg/m² PO twice daily Monday through Friday, beginning on day 1 of radiation and ending on day 28 of radiation (the final day); capecitabine will be held on weekends and during breaks in radiation for any reason (i.e. holidays, toxicity). Capecitabine dose should be rounded according to the BSA with respect to the tablet strengths.

7.4  Gemcitabine Study Agent Information

Refer to the package insert for comprehensive pharmacologic and safety information.

7.4.1  Formulation
Gemcitabine is an antineoplastic agent that is structurally related to cytarabine. It is a pyrimidine analogue that is cell-cycle specific. Gemcitabine is available commercially as a lyophilized powder in sterile vials containing 200 mg or 1 gram of gemcitabine as the hydrochloric salt (expressed as the free base) formulated with mannitol and sodium acetate.
7.4.2 **Mechanism of Action**
Gemcitabine is cytotoxic to cells undergoing DNA synthesis (S-phase) and also blocks the progression of cells through the G1/S-phase boundary. Gemcitabine is converted intracellularly to gemcitabine-5'-triphosphate, its active form. Steady-state plasma levels of gemcitabine occur within 15 minutes after starting the infusion. The elimination half-life of gemcitabine ranges from 32 to 638 minutes, depending on the age and gender of the patient and the rate of administration of gemcitabine.

7.4.3 **Preparation**
Regardless of the vial sizes, gemcitabine lyophilized powder will be reconstituted with normal saline to a final concentration of 38 mg/mL. Prior to administration, the drug is further diluted in normal saline to a final concentration as low as 0.1 mg/mL.

7.4.4 **Route of Administration**
An appropriate amount of drug will be prepared with normal saline and administered as a 30 minute Intravenous infusion. Prolongation of the infusion time beyond 60 minutes or more may result in adverse events such as hypotension. Gemcitabine half-life is influence by the length of the infusion.

7.4.5 **Adverse Events**
The major side effects observed with gemcitabine include leukopenia, thrombocytopenia, anemia, and a collection of signs and symptoms referred to collectively as a flu-like syndrome with fever, headache, rigors, nausea, diarrhea, itchy skin rash, myalgia, and anorexia. Other side effects have included fatigue, peripheral edema, and proteinuria. Less likely side effects include abnormal renal and liver function tests, vomiting, constipation, malaise, and anorexia. Rare side effects include Stevens-Johnson syndrome (severe skin reaction) and shortness of breath, cough, inflammation or scarring of the lung. Rare side effects have included hemolytic uremic syndrome/renal failure and liver failure have occurred following therapeutic gemcitabine therapy. Cardiac dysfunction (myocardial infarction, congestive heart failure, and atrial fibrillation) have been infrequently reported.

7.4.6 **Storage and Stability**
Store at controlled room temperature (20-25°C), should be handled and disposed of in a manner consistent with other anti-cancer drugs. Once the drug has been reconstituted, it should be stored at room temperature and used within 24 hours. The manufacturer recommends solutions of gemcitabine not be refrigerated as crystallization may occur.

7.4.7 **Supply**
Gemcitabine is commercially available. The use of drug(s) or combination of drugs in this protocol meet the criteria described under Title 21 CFR 312.2(b) for IND exemption

7.5 **nab-Paclitaxel (Abraxane®) Study Agent Information (7/31/14)**
Sites must refer to the package insert for detailed pharmacologic and safety information.

**Caution: Do Not Confuse nab-Paclitaxel (Abraxane) with Paclitaxel (Taxol).**

7.5.1 **Formulation**
Each single-use 50 ml vial will contain paclitaxel (100 mg) and approximately 900 mg human albumin (HA) as a stabilizer. Each vial will be labeled according to country-specific regulatory requirements for labeling of investigational products.

7.5.2 **Mechanism of Action**
nab-Paclitaxel appears to interact with tumors in a number of ways, but it is not fully understood. An advantageous PK profile and the more efficient use of albumin-based transport may contribute to the preclinical finding that nab-paclitaxel achieves a 33% higher tumor uptake relative to solvent bound-paclitaxel. Another possible contributing factor to the tumor accumulation of nab-paclitaxel is the binding of albumin to secreted protein acidic and rich in cysteine (SPARC), although the data supporting this relationship between SPARC and nab-paclitaxel remain largely correlarive at this point. nab-paclitaxel has also shown to improve intratumoral concentration of gemcitabine in murine models of pancreatic cancer, either through stromal depletion or by decreasing the primary gemcitabine-metabolizing enzyme, cytidine deaminase.
7.5.3 **Preparation**

**NOTE:** It is not a requirement to use filter needles in the preparation of, or in-line filters during the administration of nab-Paclitaxel. In any event, filters of pore-size less than 15 micrometers must not be used. nab-Paclitaxel will be reconstituted by appropriate study personnel and administered to the patient in the study site. The investigator will calculate the body surface area (BSA) of the patient in order to determine the total amount of nab-paclitaxel to be administered.

Calculate the patient’s body surface area at the beginning of the study and if the weight changes by > 10%, round up the number of vials to be reconstituted to the next higher whole number when a fractional number of vials is obtained by the above formula (e.g., if the total number of vials = 4.05 or 4.5, then 5 vials would be reconstituted).

Using sterile technique, prepare the vials for reconstitution.  
Swab the rubber stoppers with alcohol.

Reconstitute each nab-Paclitaxel vial by injecting 20 mL of 0.9% Sodium Chloride Injection, USP or equivalent into each vial over a period of not less than 1 minute.

Slowly inject the 20 mL of 0.9% Sodium Chloride Injection, USP, over a minimum of 1 minute, using the sterile syringe directing the solution flow onto the inside wall of the vial.

DO NOT INJECT the 0.9% Sodium Chloride Injection, USP solution directly onto the lyophilized cake as this will result in foaming.

Once the injection is complete, allow the vial to sit for a minimum of 5 (five) minutes to ensure proper wetting of the lyophilized cake/powder.

Gently swirl and/or invert the vial slowly for at least 2 minutes until complete dissolution of any cake/powder occurs. Rapid agitation or shaking will result in foaming.

If foaming or clumping occurs, stand solution for at least 15 minutes until foam subsides.

Each ml of reconstituted product will contain 5 mg of paclitaxel.

Calculate the exact total dosing volume of 5 mg/ml suspension required for the patient:

\[
\text{Dosing volume (ml)} = \frac{\text{Total dose (mg)}}{5 \text{ (mg/ml)}}
\]

The reconstituted sample should be milky and homogeneous without visible particulates. If unsuspended powder is visible, the vial should be gently inverted again to ensure complete resuspension, prior to use.

Once the exact volume of reconstituted nab-Paclitaxel has been withdrawn from the vials, discard any excess solution left over in accordance with standard operating procedures.

Further dilution is not necessary. Inject the calculated dosing volume of reconstituted nab-Paclitaxel suspension into an empty sterile, standard PVC IV bag using an injection port. Inject perpendicularly into the center of the injection port to avoid dislodging plastic material into the IV bag.

7.5.4 **Route of Administration**

Administer the calculated dosing volume of reconstituted nab-Paclitaxel suspension by IV infusion over 30 minutes. The use of in-line filters is not necessary. If used, in-line filters with pore sizes of < 15µ should not be used.

7.5.5 **Adverse Events**

- **Hematologic:** Myelosuppression
- **Gastrointestinal:** Nausea, diarrhea, vomiting, abdominal pain
• Heart: Arrhythmias, heart block, hypertension
• Neurological: Sensory and peripheral neuropathy
• Allergy: Severe anaphylactic reactions
• Other: Alopecia, fatigue, arthralgia, myopathy, myalgia, infiltration (erythema, induration, tenderness, rarely ulceration), hypotension, irritation to the injection site, mucositis

7.5.6 Storage and Stability
Unreconstituted nab-Paclitaxel should be stored at controlled room temperature (20° to 25°C or 68° to 77°F) in its carton. Reconstituted nab-Paclitaxel should be used immediately. If not used immediately, the vial of reconstituted nab-Paclitaxel must be placed in its carton and be placed in a refrigerator at 2°C to 8°C (36° to 46°F) for a maximum of 8 hours. Both forms should be stored in an area free of environmental extremes and must be accessible only to study personnel.

7.5.7 Supply
Celgene will supply nab-Paclitaxel free of charge to patients on study in the U.S. The use of drug(s) or combination of drugs in this protocol meet the criteria described under Title 21 CFR 312.2(b) for IND exemption

7.5.8 Drug Ordering and Accountability
Celgene will supply nab-Paclitaxel free of charge to patients on study. The drug will be distributed by a vendor, Biologics, Inc., under contract to NRG Oncology. Drug accountability records must be maintained at all sites according to good clinical practices and NCI guidelines.

The Study Agent Shipment Form (SASF); available on the NRG Oncology/RTOG web site, www.rtog.org under protocol-specific materials/regulatory resources for U.S. sites must be submitted to the CTSU Regulatory Office (Fax 215-569-0206) as soon as the individual responsible for the study agent has been identified. The completed SASF document may also be e-mailed to the CTSU at CTSURegulatory@ctsu.coccg.org.

The drug supply will not be shipped by Biologics, Inc. until the patient has been registered. NRG Oncology will notify Biologics, Inc. to initiate each of these shipments after registration of the patient. Biologics, Inc. will ship drug for pre-randomized patients and patients randomized to Arms 1-3. Pre-randomized patients will receive 27 vials of nab-Paclitaxel sufficient for 3 cycles of treatment. Randomized patients will receive 54 vials of nab-Paclitaxel sufficient for 6 cycles of treatment. Prior to completion of 6 months of treatment, Biologics will contact the study site to confirm their requirement for additional study drug.

Upon notification of a new patient enrollment, Biologics, Inc. will place an outbound call to the site contact to confirm that the site’s shipment is being processed. Biologics’ distribution team will monitor packages throughout the duration of transit via the FedEx web site and FedEx One Call Solution (live support). Real-time monitoring enables Biologics to mitigate potential delivery delays.

Biologics, Inc. will ship drug according to the following schedule:

<table>
<thead>
<tr>
<th>RTOG 1201 Shipment Schedule</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient Randomized</td>
</tr>
<tr>
<td>Monday</td>
</tr>
<tr>
<td>Tuesday</td>
</tr>
<tr>
<td>Wednesday</td>
</tr>
<tr>
<td>Thursday</td>
</tr>
<tr>
<td>Friday</td>
</tr>
</tbody>
</table>
Biologics, Inc. will ship the order “same day” for all orders received before 2 p.m. EST, Monday through Thursday via FedEx Priority Overnight. Orders received after 2 p.m. EST, Monday through Thursday will be processed and shipped the next business morning.

Drug deliveries are restricted during weekends and holidays. Biologics, Inc. observes the following holidays: New Year’s Day, Memorial Day, July 4th, Labor Day, Thanksgiving Day, the Friday following Thanksgiving Day, Christmas Eve, and Christmas Day. Sites should plan ahead to accommodate patients being treated during restricted times.

Please contact the drug distributor listed in the protocol directly for shipment tracking information and anticipated delivery dates or if a shipment has not been received by the expected date.

At the completion of the study, unused supplies will be destroyed at the site according to the institution's policy for drug destruction. Sites should complete the drug destruction form located on the NRG Oncology/RTOG web site www.rtog.org under protocol-specific materials/regulatory resources and send the form to Biologics (see below for contact information).

Questions about supply and delivery should be directed to:

Elliott Lee, Clinical Research Program Manager  
Biologics, Inc.  
Clinical Research Services  
120 Weston Oaks Court  
Cary, NC 27513-2256  
Email: elle@biologicsinc.com or clinicaltrials@biologicsinc.com  
Phone: 919-459-4990 / Toll Free 800-693-4906  
Fax: 919-256-0794

7.6 Capecitabine Information
Refer to the package insert for comprehensive pharmacologic and safety information

7.6.1 Formulation
Capecitabine is supplied as a biconvex, oblong film-coated tablet for oral administration. Only the 500 mg tablets will be utilized in this study. Dosages will be rounded to the nearest 500 mg.

7.6.2 Mechanism of Action
Capecitabine is an oral prodrug of 5-fluorouracil. Metabolized in the liver to 5’-deoxy-fluorocytidine, subsequently converted to 5’-deoxy-5-fluorouridine which is then hydrolyzed to 5-fluorouracil (active). Peak plasma levels occur in 90 minutes, and elimination half-life is 45 minutes.

7.6.3 Preparation
This is an oral agent. Food delays the time to peak plasma level by about 90 minutes, and reduces the peak plasma concentration about 60%. Despite the effects of food on capecitabine pharmacokinetics, the manufacturer recommends giving the drug at the end of a meal because established safety and efficacy data are based on administration with food.

7.6.4 Route of Administration
The capecitabine daily dose is given orally in two divided doses (approximately 12 hours apart) at the end of a meal. The tablets should be taken with water.

Patients will be asked to maintain a diary documenting self-administration of capecitabine. Prior to starting treatment, the patient will be provided with and instructed in the proper use of a pill diary (see “Non-Study Specific Forms” on the RTOG website, or http://www.rtog.org/LinkClick.aspx?fileticket=CrZv7f1tB1w%3d&tabid=308, for a pill diary template) to record their daily pill consumption. This record will be checked for compliance by the treating physician. The diary will be retained in the patient’s record for submission to RTOG ONLY upon request; i.e., diaries are not to be submitted but will be retained at the site as source documents. Patients who are non-compliant must be re-instructed in the use of the diary.
7.6.5 Potential Drug Interactions

**Antacids**
The administration of 20 mL of an antacid containing aluminum hydroxide and magnesium hydroxide may result in an increase in the area under the concentration-time curve (AUC) and maximum concentration (Cmax) of capecitabine of 16% and 35%, respectively. These changes were not considered clinically significant.

**Oral Anticoagulants**
Altered coagulation parameters and/or bleeding, including death, have been reported in patients receiving capecitabine and coumarin-derivative anticoagulants. Post marketing reports have revealed clinically significant increases in prothrombin time (PT) and INR in patients who were stabilized on anticoagulants when capecitabine was initiated. These events occurred within several days to several months after concurrent therapy was initiated. Patients receiving capecitabine and an oral anticoagulant should be closely and regularly monitored.

**Phenytoin**
Some patients receiving capecitabine and phenytoin may experience phenytoin toxicity as a result of increased phenytoin plasma levels. Phenytoin levels should be closely monitored in patients taking concomitant phenytoin and capecitabine. The dose of phenytoin may need to be reduced.  

**CYP2C9 Substrate**
Caution should be used when capecitabine is coadministered with drugs known to be CYP2C9 substrate.

7.6.6 Adverse Events

Common side effects from capecitabine include diarrhea (which may be severe), dermatologic effects (hand-and-foot syndrome referred to as palmar-plantar erythrodysesthesia), hematologic effects (neutropenia, thrombocytopenia, anemia and lymphopenia), weight gain, gastrointestinal effects (diarrhea, nausea, vomiting stomatitis, abdominal pain and constipation). Uncommon side effects include hepatotoxicity (hyperbilirubinemia). Rare side effects may include cardiovascular effects (myocardial infarction, dysrhythmias, cardiomyopathy).

7.6.7 Storage and Stability
Tablets should be stored at controlled room temperature (25°C) in tightly closed containers with excursions to 15-30°C permitted.

7.6.8 Supply
Capecitabine is commercially available. The use of drug(s) or combination of drugs in this protocol meet the criteria described under Title 21 CFR 312.2(b) for IND exemption.

7.7 Dose Modifications and Management of Toxicity (7/31/14)

7.7.1 Rules for Dose Omissions and Modified Schedules

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

**Day 8 dose is missed:**
Cycle continues per protocol, with one dose not given (i.e., 1-2-3-Rest, 1-X-3-Rest, 1-2-3-Rest, etc.). Day 8 is administered as per cycle calendar if counts and chemistries permit.

**Day 15 dose missed:**
That week becomes the week of rest. Next dose (if counts and chemistries permit) becomes Day 1 of a new cycle, and the patient is considered to have had a x2q3 (21-day) cycle (i.e., 1-2-3-Rest, 1-2-X, 1-2-3-Rest, etc.).

The maximum delay between a missed scheduled dose and the next one (whichever dose was missed) should not be longer than 21 days (except for peripheral neuropathy; see Section 7.7.4).
7.7.2 Dose Reductions for Hematologic and Non-Hematologic Toxicity
Dose adjustments are to be made according to the system showing the greatest degree of toxicity. Toxicities will be graded using CTCAE, v. 4.

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

Dose Levels

<table>
<thead>
<tr>
<th>Dose Level</th>
<th>nab-Paclitaxel (mg/m²)</th>
<th>Gemcitabine (mg/m²)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Starting Dose</td>
<td>125</td>
<td>1,000</td>
</tr>
<tr>
<td>-1</td>
<td>100</td>
<td>800</td>
</tr>
<tr>
<td>-2</td>
<td>75</td>
<td>600</td>
</tr>
</tbody>
</table>

Dose reductions may or may not be concomitant. Please refer to the tables below for day of cycle and hematologic/non-hematologic toxicity, respectively.

**A maximum of 2 dose level reductions are allowed. Patients experiencing study drug-related toxicities that require a delay in scheduled nab-Paclitaxel or gemcitabine dosing for >28 days will be discontinued from further treatment in this study (except for peripheral neuropathy).**

7.7.3 Dose Adjustments for Toxicity Within a Treatment Cycle
In the event that patients must have treatment delayed within a treatment cycle due to toxicities, those doses held during a cycle will not be made up

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

<table>
<thead>
<tr>
<th>ANC</th>
<th>Platelets</th>
<th>Timing</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥1.5X10^9/L And ≥100 x 10^⁹/L</td>
<td>Treat on time</td>
<td></td>
</tr>
<tr>
<td>&lt;1.5 x 10^9/L Or &lt; 100 x 10^⁹/L</td>
<td>Delay by 1 week intervals</td>
<td></td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>Toxicity/dose held</th>
<th>Gemcitabine + nab-Paclitaxel</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade 0, 1, 2</td>
<td>Treat on time</td>
</tr>
<tr>
<td>Grade ≥ 3</td>
<td>Delay by 1 week until improves to &lt; Grade 2, then resume at permanent 1 dose level reduction if non-heme toxicities were treatment related (In the event of persistent grade 2 toxicity, the treating investigator may choose to wait an additional week for toxicities to resolve to ≤ grade 1).</td>
</tr>
</tbody>
</table>

Dose Modifications Within A Cycle Due to Hematologic Toxicity

<table>
<thead>
<tr>
<th>Day 8</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood Counts</td>
</tr>
<tr>
<td>ANC &gt; 1000 and Platelets &gt; 75,000</td>
</tr>
<tr>
<td>ANC 500-1000 or Platelets 50,000-74,999</td>
</tr>
<tr>
<td>ANC &lt; 500 or Platelets &lt; 50,000</td>
</tr>
</tbody>
</table>
Day 15

<table>
<thead>
<tr>
<th>Blood Counts</th>
<th>nab-Paclitaxel</th>
<th>Gemcitabine</th>
</tr>
</thead>
<tbody>
<tr>
<td>ANC &gt;1000 and Platelets &gt; 75,000</td>
<td>100%</td>
<td>100%</td>
</tr>
<tr>
<td>ANC 500-1000 or Platelets 50,000-74,999</td>
<td>Temporary 1 dose level reduction (treat on time)</td>
<td>Temporary 1 dose level reduction (treat on time) **</td>
</tr>
<tr>
<td>ANC &lt; 500 or Platelets &lt; 50,000</td>
<td>Hold*</td>
<td>Hold</td>
</tr>
<tr>
<td>ANC &gt; 1000 and Platelets ≥ 75,000</td>
<td>Same dose as day 8 (treat on time)</td>
<td>Same dose as day 8 (treat on time) **</td>
</tr>
<tr>
<td>ANC 500-1000 or Platelets 50,000-74,999</td>
<td>Same dose (as Day 8, treat on time)**</td>
<td>Same dose (as Day 8, treat on time)**</td>
</tr>
<tr>
<td>ANC &lt; 500 or Platelets &lt; 50,000</td>
<td>Hold</td>
<td>Hold</td>
</tr>
<tr>
<td>ANC &gt; 1000 and Platelets &gt; 75,000</td>
<td>Decrease Day 1 dose by 1 level (treat on time)</td>
<td>Decrease Day 1 dose by 1 level (treat on time)</td>
</tr>
<tr>
<td>ANC 500-1000 or platelets 50,000-74,999</td>
<td>Decrease day 1 dose by 1 level (treat on time)**</td>
<td>Decrease day 1 dose by 1 level (treat on time)**</td>
</tr>
<tr>
<td>ANC &lt; 500 or Platelets &lt; 50,000</td>
<td>Hold</td>
<td>Hold</td>
</tr>
</tbody>
</table>

Patients requiring a hold of treatment due to ANC < 500 or Platelets < 50,000, when treatment is resumed should have a permanent 1 dose level reduction.

**Myeloid growth factors may be utilized according to standard institutional procedures.

Patients developing febrile neutropenia should have treatment held, and when treatment is resumed, on recovery from toxicities should have a permanent 1 dose level reduction. Patients developing febrile neutropenia must have ANC ≥1,500 prior to resumption of treatment.

### Dose Modifications for Non-Hematological Treatment Related Toxicity within a Cycle

<table>
<thead>
<tr>
<th>CTCAE Grade</th>
<th>Percent of Day 1 nab-Paclitaxel</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade 0-2</td>
<td>100%</td>
</tr>
<tr>
<td>Grade 3-4 (except alopecia)</td>
<td>Hold until resolution to ≤ Grade 1 then resume treatment at the next lower dose level.</td>
</tr>
</tbody>
</table>

For patients experienced non-treatment related toxicities such as a thrombosis or infection from an obstructed stent, upon resolution of toxicities, dose modifications are not required.

#### 7.7.4 Peripheral Neuropathy

nab-Paclitaxel treatment should be withheld in patients who experience ≥Grade 3 peripheral neuropathy. Gemcitabine administration can continue during this period. nab-Paclitaxel treatment may be resumed at the next lower dose level in subsequent cycles after the peripheral neuropathy improves to ≤Grade 1.

#### 7.7.5 Administration of Study Drug to Patients with Abnormal Hepatic Function

nab-paclitaxel should only be administered if total bilirubin is within the parameters established in the eligibility criteria (< 1.5x ULN). Hepatic toxicity from taxanes may occur but it is uncommon. Therefore, hepatic dysfunction that occurs while the patient is on study should prompt an evaluation to determine the cause, including the possibility of obstructive jaundice from disease or stent malfunction, metastatic disease, and hepatotoxicity from concurrent medications, alcohol use or other factors. Gemcitabine may be administered as long as the grade of hepatic toxicity is < grade 3.
7.7.6. **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). Study drug administration should be permanently discontinued upon making a diagnosis of drug induced interstitial pneumonitis.

7.7.7. **Hypersensitivity Reactions**
Hypersensitivity reactions are not expected with either nab-Paclitaxel or gemcitabine. If they do occur, minor symptoms such as flushing, skin reactions, dyspnea, 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 the causative drug administration and should not be re-challenged.

7.7.8 **Pulmonary Embolism and Deep Vein Thrombosis**
To resume administration of nab-paclitaxel in the event of a pulmonary embolism or deep-vein thrombosis, patients must be started on low molecular weight heparin or similar anticoagulation therapy. Grade 4 events must be resolved to grade $\leq 3$ within 21 days to continue nab-paclitaxel.

7.7.9 **Interstitial Pneumonitis**
While participating in this study, patients should be carefully monitored to prevent or minimize the occurrence of interstitial pneumonitis. Careful pre-study screening with continuous on-study monitoring for signs and symptoms is required. Should a patient develop symptoms of pneumonitis during this study, the timely initiation of appropriate management is required. Recommended guidelines are as follows:
1. Before enrollment, evaluate candidate patients for familial, environmental, or occupational exposure to opportunistic pathogens, and do not enroll those with a history of slowly progressive dyspnea and unproductive cough, or of conditions such as sarcoidosis, silicosis, idiopathic pulmonary fibrosis, pulmonary hypersensitivity pneumonitis, or multiple allergies.
2. During study treatment, provide close attention to episodes of transient or repeated dyspnea with unproductive persistent cough or fever. Radiographic evaluation with chest x-rays and CT scans (normal or high resolution) may be indicated to evaluate for infiltrates, ground-glass opacities, or honeycombing patterns. Pulse oximetry and pulmonary function tests can show respiratory and ventilation compromise.
3. 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.
4. Administration of nab-paclitaxel should be interrupted upon diagnosis of interstitial pneumonitis and patients permanently discontinued from further nab-paclitaxel. After ruling out an infectious etiology, intravenous high-dose corticosteroid therapy should be instituted without delay, with appropriate premedication and secondary pathogen coverage. Patients with an added immunological agent also may require immune modulation with azathioprine or cyclophosphamide. Appropriate ventilation and oxygen support should be used when required.

7.7.10 **Prophylaxis Against Sepsis**
In the metastatic pancreatic cancer phase 3 study (CA046), an increase in cases of non-neutropenic sepsis was observed with the combination of nab-paclitaxel and gemcitabine. An exploratory analysis suggested that the presence of biliary stents may have increased the risk of sepsis in that population. Investigators were to provide oral broad spectrum antibiotics to subjects who were then to initiate these antibiotics at the first occurrence of fever. Patients enrolled in this clinical trial may not have the same risk of sepsis as metastatic pancreatic cancer patients. Patients should be advised that there could be an increased risk of serious infection and they should contact their physician for evaluation when they develop a fever. Fever or similar symptoms should be fully evaluated as an early sign of a serious infection. Broad spectrum
antibiotics such as fluoroquinolones may be provided to subjects to treat or as prophylaxis for infection at the discretion of the treating physician.

7.7.11 **Dose modification for Capecitabine during Radiation Therapy**

Because they have some overlapping toxicities, is not always possible to separate radiation toxicity from capecitabine toxicity. In general, dose modifications of capecitabine are sufficient to ameliorate hematologic and non-hematologic toxicity. See below for specific guidelines for dose adjustment and supportive care of toxicities that may occur during chemoradiation.

**Hematologic Toxicity**

Capecitabine and radiation will be modified according to blood counts within 48 hours of treatment as shown in the table below. There will be no dose modifications for lymphopenia, hypoglycemia, hyperglycemia, Hb, HCT or WBC levels.

<table>
<thead>
<tr>
<th>TX DAY BLOOD COUNTS</th>
<th>PLATELETS</th>
<th>DOSAGE</th>
</tr>
</thead>
<tbody>
<tr>
<td>ANC /μl</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt; 1,000/μl and</td>
<td>&gt; 75,000/μl</td>
<td>Full dose of capecitabine</td>
</tr>
<tr>
<td>500-999/μl or</td>
<td>50,000 – 75,000/μl</td>
<td>Hold capecitabine until ANC &gt; 1,000/μl and Plt &gt; 75,000/μl then reduce by 25%</td>
</tr>
<tr>
<td>&lt; 500/μl or</td>
<td>&lt;50,000 μl</td>
<td>Hold XRT and capecitabine. When ANC &gt;1,000/μl and Plt &gt; 75,000/μl resume XRT with 25% reduction of capecitabine</td>
</tr>
</tbody>
</table>

**Additional Notes:**
- Patients who have required two dose reductions of capecitabine and experience a third episode of ANC <1,000/μl or Platelet < 75,000/μl may complete radiation but will not receive additional capecitabine

**Non-hematologic Toxicity**

Capecitabine will be held for any Grade 2 or greater non-hematologic toxicity, excluding radiation dermatitis cholangitis, DVT, and fatigue. Capecitabine will not be resumed until non-hematological toxicity has resolved to <= Grade 1. When treatment is resumed patients will receive a 25% dose reduction of capecitabine.

Dose reductions from non-hematologic toxicities during chemoradiation will be maintained during chemoradiation. If a second episode of Grade 2 or greater non-hematologic toxicity occurs, treatment again will be held until non-hematological toxicity has resolved to <= Grade 1. When treatment is resumed, patients will receive a second 25% dose reduction of capecitabine. If a fourth episode of Grade 2 or greater non-hematologic toxicity occurs, patients may complete radiation but will not receive additional capecitabine.

**Capecitabine dose modification for diarrhea during chemoradiation**

**NOTE:** Dose modifications are for capecitabine only

<table>
<thead>
<tr>
<th>DIARRHEA GRADE</th>
<th>STOOLS/DAY &gt;PRETREATMENT</th>
<th>DOSAGE</th>
</tr>
</thead>
<tbody>
<tr>
<td>CTC Grade 1</td>
<td>(2-3 stools/day)</td>
<td>Maintain dose</td>
</tr>
<tr>
<td>CTC Grade 2</td>
<td>(4-6 stools/day)</td>
<td>Discontinue until Grade 1 or lower and restart according to number of appearances of &gt;= Grade 2 toxicity: 1st = Reduce dose by 25% of prior dose 2nd = Reduce by 25% of prior dose</td>
</tr>
</tbody>
</table>


<table>
<thead>
<tr>
<th>CTC Grade 3</th>
<th>( &gt; 7 stools/day)</th>
<th>Discontinue until Grade 1 or lower and restart according to number of appearances of ≥ Grade 2 toxicity: 1st = 75% of capecitabine starting dose 2nd = 50% of capecitabine starting dose 3rd = 50% of capecitabine starting dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>CTC Grade 4</td>
<td>Life threatening</td>
<td>Discontinue capecitabine</td>
</tr>
</tbody>
</table>

Hand Foot Syndrome (HFS)

Patients experiencing grade 2 or greater HFS will have capecitabine treatment withheld until the toxicity resolves to grade 1 or less, then reinstituted at a 25% dose reduction of capecitabine. If a second (or third) episode of Grade 2 or greater HFS occurs, treatment again will be held until toxicity resolves to grade 1 or less. When treatment is resumed, patients will receive a second (or third) 25% dose reduction of capecitabine. If a fourth episode of Grade 2 or greater HFS toxicity occurs, patients may complete radiation but will not receive additional capecitabine.

Management of Diarrhea during Chemoradiation

Capecitabine induced diarrhea and management

A three-step plan to manage diarrhea will be used. The goal will be to keep the frequency of bowel movements to less than four per day:

- **Step 1**: Take Lomotil as needed. When no longer sufficient to control the increased frequency of bowel movement, patients go to step 2
- **Step 2**: Take 2 Lomotil every 3-4 hours
- **Step 3**: Subsequently, Imodium is added and alternated with Lomotil, which is step 3; 2 tablets of one or the other is taken every 2-3 hours

**Additional measures:** Delayed and immediate release narcotics will be used at the discretion of the treating physician. Infectious diarrhea must be considered as an etiology, particularly if diarrhea occurs during the first two weeks of radiation. Outpatient intravenous rehydration will be given in patients who become dehydrated.

7.8 **Standard hydration/antiemetic regimen**

IV hydration required at the medical or radiation oncologist's discretion. Standard of care orders for premedications (antiemetics) and hydration should be at the discretion of the medical oncologist.

7.9 **Modality Review**

The Medical Oncology Co-Chair, Gauri Varadhachary, MD, will perform a Chemotherapy Assurance Review of all patients who receive or are to receive chemotherapy in this trial. The goal of the review is to evaluate protocol compliance. The review process is contingent on timely submission of chemotherapy treatment data as specified in Section 12.1. The scoring mechanism is: Per Protocol/Acceptable Variation, Unacceptable Deviation, and Not Evaluable. A report is sent to each institution once per year to notify the institution about compliance for each case reviewed in that year.

The Medical Oncology Co-Chair, Gauri Varadhachary, MD will perform a Quality Assurance Review after complete data for the first 10 cases enrolled has been received at NRG Oncology. Dr. Varadhachary will perform the next review after complete data for the next 20 cases enrolled has been received at NRG Oncology. The final cases will be reviewed within 3 months after this study has reached the target accrual or as soon as complete data for all cases enrolled has been received at NRG Oncology, whichever occurs first.
7.10 Adverse Events (7/31/14)
This study will utilize the NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 for adverse event (AE) reporting. The CTCAE version 4.0 is located on the CTEP website at http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm. All appropriate treatment areas should have access to a copy of the CTCAE version 4.0.

Adverse events (AEs) that meet expedited reporting criteria defined in the table(s) below will be reported via the CTEP-AERS (CTEP Adverse Event Reporting System) application accessed via the CTEP web site (https://eapps-ctep.nci.nih.gov/ctepaers/pages/task?rand=1390853489613).

In the rare event when Internet connectivity is disrupted, a 24-hour notification must be made to NRG Oncology at 1-800-227-5463, ext. 4189, for instances when Internet fails. Once internet connectivity is restored, an AE report submitted by phone must be entered electronically into CTEP-AERS.

7.10.1 Adverse Events (AEs)
**Definition of an AE:** Any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related. Therefore, an AE can be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not considered related to the medicinal (investigational) product (attribution of unrelated, unlikely, possible, probable, or definite). (International Conference on Harmonisation [ICH], E2A, E6). [CTEP, NCI Guidelines: Adverse Event Reporting Requirements. February 29, 2012; http://ctep.cancer.gov/protocolDevelopment/electronic_applications/adverse_events.htm]

7.10.2 Serious Adverse Events (SAEs)
Serious adverse events (SAEs) as defined in the table below will be reported via CTEP-AERS. SAEs that require 24 hour notification are defined in the expedited reporting table below. Contact the CTEP-AERS Help Desk if assistance is required.

**Definition of an SAE:** Any adverse drug event (experience) occurring at any dose that results in any of the following outcomes:

- Death;
- A life-threatening adverse drug experience;
- Inpatient hospitalization or prolongation of existing hospitalization;
- A persistent or significant disability/incapacity;
- A congenital anomaly/birth defect.
- Important medical events that may not result in death, be life threatening, or require hospitalization may be considered an SAE, when, based upon medical judgment, they may jeopardize the patient and may require medical or surgical intervention to prevent one of the outcomes listed in the definition.

Due to the risk of intrauterine exposure of a fetus to potentially teratogenic agents, the pregnancy of a study participant must be reported via CTEP-AERS in an expedited manner.

7.10.3 Acute Myeloid Leukemia (AML) or Myelodysplastic Syndrome (MDS)
AML or MDS that is diagnosed as a secondary malignancy during or subsequent to treatment in patients on NCI/CTEP-sponsored clinical trials must be reported via the CTEP-AERS system within 30 days of AML/MDS diagnosis.

**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.

- 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 the routine reporting mechanisms outlined in each protocol.

**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 via CDUS unless otherwise specified.

### 7.11 CTEP-AERS Expedited Reporting Requirements

All serious adverse events that meet expedited reporting criteria defined in the reporting table below will be reported via CTEP-AERS, the CTEP Adverse Event Reporting System, accessed via the CTEP web site, [https://eapps-ctep.nci.nih.gov/ctepaers/pages/task?rand=1390853489613](https://eapps-ctep.nci.nih.gov/ctepaers/pages/task?rand=1390853489613).

Submitting a report via CTEP-AERS serves as notification to NRG and satisfies NRG requirements for expedited adverse event reporting.

CTEP-AERS provides a radiation therapy-only pathway for events experienced that involve radiation therapy only. These events must be reported via the CTEP-AERS radiation therapy-only pathway.

In the rare event when Internet connectivity is disrupted, a 24-hour notification must be made to the NRG Oncology at 1-800-227-5463, ext. 4189, for instances when Internet fails. Once internet connectivity is restored, an AE report submitted by phone must be entered electronically into CTEP-AERS.

- **CTEP-AERS-24 Hour Notification** requires that a CTEP-AERS 24-hour notification is electronically submitted within 24 hours of learning of the adverse event. Each CTEP-AERS 24-hour notification must be followed by a CTEP-AERS 5 Calendar Day Report. Serious adverse events that require 24 hour CTEP-AERS notification are defined in the expedited reporting table below.
- **Supporting source document** is not mandatory. However, if the CTEP-AERS report indicates in the *Additional Information* section that source documentation will be provided, then it is expected. If supporting source documentation accompanies a CTEP-AERS report, include the protocol number, patient ID number, and CTEP-AERS ticket number on each page, and fax supporting documentation to the NRG Oncology dedicated SAE FAX, 215-717-0990.
- **A serious adverse event** that meets expedited reporting criteria outlined in the following table but is assessed by the CTEP-AERS System as “expedited reporting NOT required” must still be reported to fulfill RTOG safety reporting obligations. Sites must bypass the “NOT Required” assessment; the CTEP-AERS System allows submission of all reports regardless of the results of the assessment.

CTEP defines expedited AE reporting requirements for late phase 2 and phase 3 trials as described in the table below. **Important:** All AEs reported via CTEP-AERS also must be reported on the AE section of the appropriate case report form (see [Section 12.1](#)).
Late Phase 2 and Phase 3 Studies: Expedited Reporting Requirements for Adverse Events that Occur on Studies Utilizing a Commercially Available Agent within 30 Days of the Last Administration of the Commercially Available Agent

**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 $\geq 24$ 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 CTEP-AERS within the timeframes detailed in the table below.

<table>
<thead>
<tr>
<th>Hospitalization</th>
<th>Grade 1 Timeframes</th>
<th>Grade 2 Timeframes</th>
<th>Grade 3 Timeframes</th>
<th>Grade 4 &amp; 5 Timeframes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Resulting in Hospitalization $\geq 24$ hrs</td>
<td>10 Calendar Days</td>
<td></td>
<td></td>
<td>24-Hour 5 Calendar Days</td>
</tr>
<tr>
<td>Not resulting in Hospitalization $\geq 24$ hrs</td>
<td>Not required</td>
<td></td>
<td>10 Calendar Days</td>
<td></td>
</tr>
</tbody>
</table>

**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 reported via CTEP-AERS 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 within 10 calendar days of learning of the AE.

 Serious adverse events that occur more than 30 days after the last administration of the commercially available agent 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

For studies using PET or SPECT IND agents, the AE reporting period is limited to 10 radioactive
8.0 SURGERY
Not applicable to this study.

9.0 OTHER THERAPY

9.1 Permitted Supportive Therapy
All supportive therapy for optimal medical care will be given during the study period at the discretion of the attending physician(s) within the parameters of the protocol and documented on each site’s source documents as concomitant medication.

9.1.1 Appetite stimulants: Megace, oxandrin or mirtazapine

9.1.2 Antiemetics (See Section 7.10 for standard hydration/antiemetic regimen

9.1.3 Anticoagulants

9.1.4 Antidiarrheals (Imodium, Lomotil, octreotide) (See Section 7.9 for diarrhea management)

9.1.5 Pancreatic enzymes such as Creon should be prescribed when malabsorption, diarrhea or abdominal cramps is a problem

9.1.6 Pain interferes with effective delivery of therapy and should be managed aggressively. Non-opiates and opiates and a celiac nerve block should be prescribed as needed

9.1.7 Hematopoietic Growth Factors

9.1.8 Nutritional supplementation

9.1.9 Antacids or proton pump inhibitors: zantac, lansoprazole, omeprazole, pantoprazole sodium, or rabeprazole sodium. If any new epigastric pain develops, ulceration should be suspected and sucralfate should be started. Upper endoscopy should be performed as clinically directed

9.1.10 Anti-depressants

9.2 Non-permitted Supportive Therapy
None

10.0 TISSUE/SPECIMEN SUBMISSION (7/31/14)

10.1 General Information
Central pathology review for analysis of SMAD 4 status is mandatory for this study. Specimens for central review will first be sent to Memorial Sloan-Kettering Cancer Center to minimize the time interval between Step 1 and Step 2 randomization. After central review is completed at Memorial Sloan-Kettering, any remaining tissue from patients who have consented to banking will be shipped from Memorial Sloan-Kettering to the NRG Oncology Biospecimen Resource at the University of California San Francisco for tissue banking and future translational research (highly recommended but not mandatory) (See Section 10.3). Tissue from non-consenting patients will be returned to the submitting institution (See Section 10.2).

The NRG Oncology Biospecimen Resource at the University of California San Francisco acquires and maintains high quality specimens from NRG Oncology trials. Tissue from each block is preserved through careful block storage and processing. NRG Oncology encourages participants in protocol studies to consent to the banking of their tissue. The NRG Oncology Biospecimen Resource provides tissue specimens to investigators for translational research studies. Translational research studies integrate the newest research findings into current protocols to investigate important biologic questions.

10.2 Specimen Collection For Central Review and analysis of SMAD 4 status (Mandatory)

10.2.1 Central Review will be performed for every case by Christine Iacobuzio-Donahue, MD, PhD and/or her designee at Memorial Sloan-Kettering Cancer Center.
The following material **must** be provided as soon as possible following Step 1 registration to achieve rapid and efficient SMAD4 testing, as the SMAD 4 results are required for Step 2 randomization:

- Formalin fixed and paraffin embedded cell block or core tissue biopsy. A core biopsy is the preferred method. If the cell block or core biopsy cannot be released from the institution, then five (5) unstained slides of the cell block or core biopsy will also suffice. For patients with surgical blocks (a 2 mm diameter core of tumor tissue punched from the tissue block containing the tumor with a punch tool and submitted in a plastic tube labeled with the surgical pathology number is recommended if the site cannot supply the block itself. **NOTE:** A kit with the punch, tube, and instructions can be obtained free of charge from the NRG Oncology Biospecimen Resource. Block or core must be clearly labeled with the pathology identification number that corresponds to the Pathology Report.

- One H&E stained slide section corresponding to the cell block or core biopsy paraffin block is also required for confirmation of the presence of carcinoma in the specimen.

**NOTE:** FNA smears cannot be used to determine SMAD4 expression by immunohistochemistry

- A Pathology Report documenting that the submitted block, core, or unstained slides contain tumor; the report must include the NRG Oncology protocol number and patient’s case number. The patient’s name and/or other identifying information should be removed from the report. All other information must NOT be removed from the report.

- A Specimen Form (SP) must accompany the tissue that is being submitted for SMAD 4 testing. If the patient has consented to the optional tissue/specimen collection, the standard Specimen Transmittal Form (ST) and pathology report must also accompany the specimen. The forms must include the NRG Oncology protocol number and the patient’s case number. The SP form must be filled out completely and indicate whether the patient has consented to banking of any leftover tissue for tissue banking/translational research. The ST form is the standard form required for the optional tissue/specimen collection and it will be forwarded by Memorial Sloan-Kettering Cancer Center to the NRG Oncology Biospecimen Resource with the remaining tissue after SMAD4 testing is complete for those patients who consented to tissue banking.

**10.2.2 Determination of SMAD4 Status:**

To determine SMAD4 status, immunolabeling for SMAD4 protein will be performed in a CLIA certified laboratory at Memorial Sloan-Kettering using a 1:100 dilution of anti-SMAD4 clone B8 (Santa Cruz Biotechnology, Santa Cruz, CA). Immunohistochemical labeling of SMAD4 will be scored as intact (positive) if positive nuclear labeling is observed of the neoplastic cells or loss (negative) if no labeling is observed of the neoplastic cells. Only sections in which internal controls (lymphocytes, stromal cells, islets etc.) present on the same slide which show a normal pattern of SMAD4 nuclear labeling will be used.

**10.2.3 Send central review pathology materials overnight (labeled “RTOG 1201”) directly to:**

Christine Iacobuzio-Donahue MD, PhD  
Memorial Sloan Kettering Cancer Center  
417 E. 68th Street, Z-763  
New York, NY 10065  
Tel: 646-888-2239  
Fax: 646-888-3235  
iacobuzc@mskcc.org

- Notify Dr. Iacobuzio-Donahue by e-mail on the day of submission with the following information: (1) that a case is being submitted for review and the NRG Oncology case number;  
(2) the overnight shipping carrier and tracking number, and (3) e-mail and phone number of contact person.
10.3 Specimen Collection for Tissue Banking/Translational Research (Highly recommended) (7/31/14)
For patients who have consented to participate in the tissue/blood component of the study.

NOTE: Patients must be offered the opportunity to participate in the banking components of the study. If the patient consents to participate in the tissue/specimen component of the study, the site is required to submit the patient’s specimens for banking as detailed below.

NOTE: Sites are not permitted to delete the tissue/specimen component from the protocol or from the sample consent.

See Appendix VI for detailed collection instructions, including information pertaining to collection kits. Note: Kits can be requested from the NRG Oncology Biospecimen Resource, RTOG@ucsf.edu, and include a pre-paid shipping label for shipment of frozen biospecimens.

The following must be provided in order for the case to be evaluable for the NRG Oncology Biospecimen Resource:

10.3.1 One H&E stained slide (can be the same one submitted for central review)
10.3.2 A formalin fixed and paraffin embedded cell block or core tissue biopsy (can be the same one submitted for central review). If the cell block or core biopsy cannot be released from the institution, then five (5) unstained slides (in addition to those provided for central review) or a 2 mm diameter core of tumor tissue punched from the tissue block containing the tumor with a punch tool and submitted in a plastic tube labeled with the surgical pathology number.

Note: A kit with the punch, tube, and instructions can be obtained free of charge from the NRG Oncology Biospecimen Resource. Block or core must be clearly labeled with the pathology identification number and block number that correspond to the Pathology Report.

10.3.3 At least one fine needle aspirate (FNA) slide of the patients tumor stained by routine methods.
10.3.4 At least one ethanol fixed, unstained fine needle aspirate (FNA) slide of the patients tumor
10.3.5 A Pathology Report documenting that the submitted block, core and/or FNA contains tumor. The report must include the NRG Oncology protocol number and patient’s case number. The patient’s name and/or other identifying information should be removed from the report. The surgical pathology numbers and information must NOT be removed from the report.

10.3.6 A Specimen Transmittal Form (ST) clearly stating that tissue is being submitted for the NRG Oncology Biospecimen Resource must be included with the shipment; if for translational research, this should be stated on the form. The ST must also document the date of collection, time point of collection of the biospecimen; the NRG Oncology protocol number, the patient’s case number, and method and time point of storage (for example, stored at -80°C for 3 days).

10.3.7 Serum and plasma will be collected prior to the start of systemic chemotherapy, Post systemic chemotherapy, but within 4 weeks prior to the start of chemoradiation and 21-42 days following chemoradiation. Whole blood will be collected pre-treatment. If a site misses the pre-treatment collection time point, they may collect the whole blood specimen at any time during treatment or at follow up. See Appendix VI for kit request, shipping and processing information.

10.3.8 Storage Conditions
Store frozen specimens at -80°C (-70°C to -90°C) until ready to ship. If a -80°C Freezer is not available:

- Samples can be stored short term in a -20°C freezer (non-frost free preferred) for up to one week (please ship out Monday-Wednesday only; Canada: Monday-Tuesday).

OR:
- Samples can be stored in plenty of dry ice for up to one week, replenishing daily (ship out Monday-Wednesday only; Canada: Monday-Tuesday).

**OR:**
- Samples can be stored in liquid nitrogen vapor phase (ship out Monday-Wednesday only; Canada: Monday-Tuesday).

Please indicate on Specimen Transmittal Form (ST) the storage conditions used and time stored.

### 10.3.9 Specimen Collection Summary

<table>
<thead>
<tr>
<th>Specimens take from patient</th>
<th>Collected When</th>
<th>Submitted As</th>
<th>Shipped How:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Central Pathology Review (MANDATORY)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>A paraffin-embedded tissue block, a 2 mm diameter core of tissue punched from the paraffin tissue block with a punch tool. a core biopsy and/or cell block prepared from the primary tumor taken before initiation of treatment. <strong>NOTE:</strong> A core biopsy is the preferred method. If the cell block or core biopsy cannot be released from the institution, then five (5) unstained slides of the cell block or core biopsy is acceptable.</td>
<td>Pre-treatment</td>
<td>Paraffin-embedded tissue block, punch biopsy, core biopsy or cell block</td>
<td>Overnight To Dr. Iacobuzio-Donahue Block or punch shipped ambient.</td>
</tr>
<tr>
<td>One H&amp;E stained slide section corresponding to the cell block or core biopsy paraffin block is also required for confirmation of the presence of carcinoma in the specimen.</td>
<td>Pre-treatment</td>
<td>H&amp;E stained slide Pre-treatment</td>
<td>Overnight To Dr. Iacobuzio-Donahue Slide shipped ambient.</td>
</tr>
</tbody>
</table>

### Specimens for Tissue Banking/Translational Research (Highly Recommended)

<table>
<thead>
<tr>
<th>Specimens taken from patient:</th>
<th>Collected when:</th>
<th>Submitted as:</th>
<th>Shipped How:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Representative H&amp;E stained slides of the primary tumor</td>
<td>Pre-treatment</td>
<td>H&amp;E stained slide [<strong>NOTE:</strong> Can be taken from same material as submitted for Central Review above]</td>
<td>Slides from central review will be sent to the NRG Oncology BSB from Memorial Sloan-Kettering. Additional slides are to be shipped to the NRG Oncology BSB Slide shipped ambient.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Specimens taken from patient:</th>
<th>Collected when:</th>
<th>Submitted as:</th>
<th>Shipped How:</th>
</tr>
</thead>
<tbody>
<tr>
<td>A paraffin-embedded tissue block, a 2 mm diameter core of tissue punched from the paraffin tissue block with a punch tool. a core biopsy and/or cell block prepared from the primary tumor taken before initiation of treatment</td>
<td>Pre-treatment</td>
<td>Paraffin-embedded tissue block, punch biopsy, core biopsy or cell block (must match the H&amp;E slide being submitted). <strong>NOTE:</strong> Can be from same material as submitted for Central Review above</td>
<td>Blocks from central review will be sent to the RTOG BSR from Memorial Sloan-Kettering. Additional FFPE material is to be shipped to the NRG Oncology BSB Block or punch shipped ambient or with cold packs during warmer months.</td>
</tr>
<tr>
<td>Test Type</td>
<td>Required Step(s)</td>
<td>Container Information</td>
<td>Shipping Information</td>
</tr>
<tr>
<td>-----------------------------------------------</td>
<td>------------------------------------------------------</td>
<td>-------------------------------------------------------------</td>
<td>-----------------------------------------------</td>
</tr>
<tr>
<td>Fine needle aspirate stained by routine cytopathology methods</td>
<td>Pre-treatment or at the time of diagnostic biopsy</td>
<td>FNA stained slide</td>
<td>TO NRG Oncology BSB Slide shipped ambient</td>
</tr>
<tr>
<td>Fine needle aspirate unstained slide- ethanol fixed</td>
<td>Pre-treatment or at the time of diagnostic biopsy.</td>
<td>Ethanol fixed FNA unstained slide</td>
<td>TO NRG Oncology BSB Slides shipped ambient</td>
</tr>
<tr>
<td>SERUM: 5-10 mL of whole blood in 1 red-top tube and centrifuge</td>
<td>(1) Pre-treatment: Prior to start of step 1 chemotherapy (gem/nab-P), (2) During treatment: During cycle 4 of gem/nab-P chemotherapy (3) Post-treatment: 21-42 days following completion of chemoradiation (Arms 1 and 2) OR during cycle 6 of gem/nab-P maintenance chemotherapy (Arm 3)</td>
<td>Frozen serum samples containing 0.5 mL per aliquot in 1 mL cryovials (five to ten)</td>
<td>To NRG Oncology BSB Serum sent frozen on dry ice via overnight carrier</td>
</tr>
<tr>
<td>PLASMA: 5-10 mL of anticoagulated whole blood in EDTA tube #1 (purple/lavender top) and centrifuge</td>
<td>(1) Pre-treatment: Prior to start of step 1 chemotherapy (gem/nab-P), (2) During treatment: During cycle 4 of gem/nab-P chemotherapy (3) Post-treatment: 21-42 days following completion of chemoradiation (Arms 1 and 2) OR during cycle 6 of gem/nab-P maintenance chemotherapy (Arm 3)</td>
<td>Frozen plasma samples containing 0.5 mL per aliquot in 1 mL cryovials (five to ten)</td>
<td>Plasma sent frozen on dry ice via overnight carrier</td>
</tr>
<tr>
<td>Whole blood for DNA: 5-10 mL of anticoagulated whole blood in EDTA tube #2 (purple/lavender top) and mix</td>
<td>Pre-treatment Note: If site missed this collection time point they may collect whole blood for DNA at a later time point instead but must note this on the ST.</td>
<td>Frozen whole blood samples containing 1 mL per aliquot in 1 mL cryovials (three to five)</td>
<td>Whole blood sent frozen on dry ice via overnight carrier</td>
</tr>
</tbody>
</table>
10.3.10 Submit materials as follows:

For Central Review (labeled “RTOG 1201”) overnight directly to:
Christine Iacobuzio-Donahue MD PhD
Memorial Sloan Kettering Cancer Center
417 E. 68th Street, Z-763
New York, NY 10065
Tel: 646-888-2239
Fax: 646-888-3235
iacobuzc@mskcc.org

For Tissue Banking and Translational Research:
U. S. Postal Service Mailing Address: For Non-frozen, Non-urgent Specimens Only
NRG Oncology Biospecimen Resource
University of California San Francisco
UCSF Box 1800
2340 Sutter Street, Room S341
San Francisco, CA 94143-1800

Courier Address (FedEx, UPS, etc.): For Trackable FFPE and ALL Frozen Specimens
NRG Oncology Biospecimen Resource
University of California San Francisco
2340 Sutter Street, Room S341
San Francisco, CA 94115

Questions: 415-476-7864/FAX 415-476-5271; RTOG@ucsf.edu

10.4 Reimbursement (7/31/14)
This information will be made available with the other registration materials in the Oncology
Patient Enrollment Network (OPEN) portal system. OPEN will serve as the registration system for
all patient enrollments onto NCI-sponsored NCTN trials, including this study, which will be
transitioned into the new Program from the NCI-sponsored Cooperative Group Clinical Trials
Program.

10.5 Confidentiality/Storage
(See the Patient Tissue Consent Frequently Asked Questions,
http://www.rtog.org/Researchers/BiospecimenResource/BiospecimenResourceFAQs.aspx for
further details.)

10.5.1 Upon receipt, the specimen is labeled with the NRG Oncology protocol number and the patient’s
case number only. The NRG Oncology Biospecimen Resource database only includes the
following information: the number of specimens received, the date the specimens were received,
documentation of material sent to a qualified investigator, type of material sent, and the date the
specimens were sent to the investigator. No clinical information is kept in the database.

10.5.2 Specimens for tissue banking will be stored for an indefinite period of time. Specimens for central
review will be retained until the study is terminated. Specimens for the translational research
component of this protocol will be retained until the study is terminated, unless the patient has
consented to storage for future studies. If at any time the patient withdraws consent to store and
use specimens, the material will be returned to the institution that submitted it.

11.0 PATIENT ASSESSMENTS
11.1 Study Parameters
See Appendix I.

11.2 Measurement of Response (7/31/14)
Freedom from local progression is an important endpoint of this study and is notoriously difficult
to assess in unresectable pancreatic cancer. It is important that the same method of assessment
Note: The first post-treatment scan cannot be used to declare local progression because early post-treatment changes may mimic local progression. Local progression can be declared and dated back to the first scan only if the subsequent scan confirms local progression.

11.3 Measurement/Definition of Progression/Recurrence
Local progression: At least a 20% increase in the sum of diameters of the primary, taking as reference the baseline sum. Given the inherent inaccuracy in determining size of a primary pancreatic carcinoma, in addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm and progression must be demonstrated on at least two sequential scans. (See Appendix I for scanning intervals)

11.4 Criteria for Discontinuation of Protocol Treatment
- Progression of disease;
- Adverse events, per Section 7.0. Note that when systemic chemotherapy prior to chemoradiation is discontinued, patients may proceed with chemoradiation
- Delays in protocol treatment > 4 weeks

If protocol treatment is discontinued, follow up and data collection will continue as specified in the protocol.

12.0 DATA COLLECTION
12.1 Medidata Rave® (7/31/14)
This study will utilize Medidata Rave® for remote data capture (RDC) of all data. Access to the trial in Rave is granted through the iMedidata application (https://login.imedidata.com) to all persons with the appropriate roles in RSS. To access iMedidata/Rave see Section 5.0 of the protocol.

In addition, site users that are a member of the RTOG must have an up to date CTEP-IAM account and have been assigned the appropriate Rave roles (Rave CRA, Read-Only, Site Investigator) in RSS at the enrolling site.

Each person responsible for data entry must be on the NRG Oncology roster in order to receive access to Medidata Rave®.

Upon initial site registration approval for the study in RSS (Regulatory Support System), all persons with Rave roles assigned on the appropriate roster will be sent a study invitation e-mail from iMedidata (iMedidata-Notification@mdsol.com) to activate their account. To accept the invitation, site users must log into the Select Login (https://login.imedidata.com/selectlogin) using their CTEP-IAM user name and password, and click on the “accept” link in the upper right-corner of the iMedidata page. Once an account is activated, eLearning modules will be available for Rave RDC instructions. Please note, site users will not be able to access the study in Rave until all required Medidata and study specific trainings are completed. Trainings will be listed in the upper right pane of the iMedidata screen.

Users that have not previously activated their iMedidata/Rave accounts will also receive a separate invitation from iMedidata to activate their account. Account activation instructions are located on the CTSU website, Rave tab under the Rave resource materials (Medidata Account Activation and Study Invitation Acceptance). Additional information on iMedidata/Rave is available on the CTSU website under the Rave tab at www.ctsu.org/RAVE/ or by contacting the CTSU Help Desk at 1-888-823-5923 or by e-mail at ctsucontact@westat.com.

12.1.1 Summary of Data Submission (11/3/14)
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 during the trial using Medidata Rave. Additionally, certain adverse events must be reported
in an expedited manner for timelier monitoring of patient safety and care. The following sections
provide information about expedited reporting. For this trial the Protocol Specific Adverse Events
and Other Adverse Events are used for routine AE reporting in Rave.

<table>
<thead>
<tr>
<th>Folder</th>
<th>Form/Item</th>
</tr>
</thead>
<tbody>
<tr>
<td>Registration via the OPEN System</td>
<td></td>
</tr>
<tr>
<td></td>
<td>● Subject Enrollment Form</td>
</tr>
<tr>
<td>Enrollment</td>
<td></td>
</tr>
<tr>
<td>When pushed into RAVE there will</td>
<td></td>
</tr>
<tr>
<td>be 5 forms representing</td>
<td></td>
</tr>
<tr>
<td>registration</td>
<td></td>
</tr>
<tr>
<td></td>
<td>● Demography Form</td>
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<tr>
<td></td>
<td>● Step Information Form</td>
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<tr>
<td></td>
<td>● Treatment Assignment Form</td>
</tr>
<tr>
<td></td>
<td>● Eligibility Checklist Form</td>
</tr>
<tr>
<td></td>
<td>● Eligibility Checklist II Form</td>
</tr>
<tr>
<td>Baseline</td>
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</tr>
<tr>
<td></td>
<td>● Patient History Form (formerly known</td>
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<tr>
<td></td>
<td>as the A5)</td>
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<tr>
<td></td>
<td>● Work Up</td>
</tr>
<tr>
<td></td>
<td>● Baseline Labs</td>
</tr>
<tr>
<td></td>
<td>● Staging</td>
</tr>
<tr>
<td></td>
<td>● Surgical pathology note (Upload of</td>
</tr>
<tr>
<td></td>
<td>report required)</td>
</tr>
<tr>
<td></td>
<td>● Prior Treatment</td>
</tr>
<tr>
<td></td>
<td>● Exclusion Criteria</td>
</tr>
<tr>
<td></td>
<td>● Supportive Care</td>
</tr>
<tr>
<td>Pre-Randomization Cycle 1-3</td>
<td></td>
</tr>
<tr>
<td></td>
<td>● Gemcitabine</td>
</tr>
<tr>
<td></td>
<td>● nab-Paclitaxel</td>
</tr>
<tr>
<td></td>
<td>● Adverse Events</td>
</tr>
<tr>
<td></td>
<td>● Treatment Labs</td>
</tr>
<tr>
<td>Restaging</td>
<td></td>
</tr>
<tr>
<td></td>
<td>● Pre-concurrent Labs</td>
</tr>
<tr>
<td></td>
<td>● Restaging CT/MRI</td>
</tr>
<tr>
<td></td>
<td>● Restaging</td>
</tr>
<tr>
<td>Pre-Randomization Follow up (for</td>
<td></td>
</tr>
<tr>
<td>nonrandomized patients)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>● Adverse Events</td>
</tr>
<tr>
<td></td>
<td>● Post-Treatment Labs</td>
</tr>
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</table>

ARMS 1 and 2

<table>
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<th>Form/Item</th>
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<tbody>
<tr>
<td>Cycle 1 – Arm 1 and 2</td>
<td></td>
</tr>
<tr>
<td></td>
<td>● Gemcitabine</td>
</tr>
<tr>
<td></td>
<td>● nab-Paclitaxel</td>
</tr>
<tr>
<td></td>
<td>● Adverse Events</td>
</tr>
<tr>
<td></td>
<td>● Treatment Labs</td>
</tr>
<tr>
<td>RT Digital Data</td>
<td></td>
</tr>
<tr>
<td></td>
<td>● Digital Data RT Plan -Pancreas</td>
</tr>
<tr>
<td></td>
<td>Protocol CT Upload</td>
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<tr>
<td>Concurrent</td>
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<td></td>
<td>● Capecitabine</td>
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<tr>
<td>Folder</td>
<td>Form/Item</td>
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<tr>
<td>---------------------------</td>
<td>------------------------------------------------</td>
</tr>
<tr>
<td>Cycles 1-4</td>
<td>• Gemcitabine</td>
</tr>
<tr>
<td></td>
<td>• nab-Paclitaxel</td>
</tr>
<tr>
<td></td>
<td>• Adverse Events</td>
</tr>
<tr>
<td></td>
<td>• Treatment Labs</td>
</tr>
<tr>
<td></td>
<td>• Supportive Care (Cycle 3 only)</td>
</tr>
</tbody>
</table>

| Follow up 1 and q 3 months thereafter | Patient Contact                                  |
|                                       | • Follow up (if patient contact=yes)             |
|                                       | • Disease assessment (if disease assessed by imaging = yes) |
|                                       | • Non protocol Tx (if non protocol TX=yes)       |
|                                       | • New Primary cancer (if new primary cancer=yes) |
|                                       | • Primary COD (if status= dead)                  |
|                                       | • COD details (if status=dead)                   |
|                                       | • Gemcitabine(if treatment continuing=yes)       |
|                                       | • nab-Paclitaxel(if treatment continuing=yes)    |
|                                       | • Labs                                          |
|                                       | • Adverse Events                                |
|                                       | • Supportive Care (Follow up 2 only)             |

<table>
<thead>
<tr>
<th>ARM 3</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Folder</td>
<td>Form/Item</td>
</tr>
<tr>
<td>Cycles 1-4</td>
<td>• Gemcitabine</td>
</tr>
<tr>
<td></td>
<td>• nab-Paclitaxel</td>
</tr>
<tr>
<td></td>
<td>• Adverse Events</td>
</tr>
<tr>
<td></td>
<td>• Treatment Labs</td>
</tr>
<tr>
<td></td>
<td>• Supportive Care (Cycle 3 only)</td>
</tr>
</tbody>
</table>

Follow up 1 and q 3 months thereafter

| Patient Contact                                  |
| • Follow up (if patient contact=yes)             |
| • Disease assessment (if disease assessed by imaging = yes) |
| • Non protocol Tx (if non protocol TX=yes)       |
| • New Primary cancer (if new primary cancer=yes) |
| • Primary COD (if status= dead)                  |
| • COD details (if status=dead)                   |
| • Gemcitabine(if treatment continuing=yes)       |
| • nab-Paclitaxel(if treatment continuing=yes)    |
| • Labs                                          |
| • Adverse Events                                |
| • Supportive Care (Follow up 2 only)             |
12.2 Summary of Dosimetry Digital Data Submission (7/31/14)
(Submit to TRIAD; See Section 5.2 for account access and installation instructions)

<table>
<thead>
<tr>
<th>Item</th>
<th>Due</th>
</tr>
</thead>
<tbody>
<tr>
<td>Preliminary Dosimetry Information (DD)</td>
<td>No later than 2 weeks PRIOR to treatment start</td>
</tr>
<tr>
<td>Digital Data Submission – Treatment Plan submitted to TRIAD by Physicist</td>
<td></td>
</tr>
<tr>
<td>Digital data submission includes the following:</td>
<td></td>
</tr>
<tr>
<td>• CT data, critical normal structures, all GTV, CTV, and PTV contours</td>
<td></td>
</tr>
<tr>
<td>• Digital beam geometry for beam sets</td>
<td></td>
</tr>
<tr>
<td>• Doses for concurrently treated beams</td>
<td></td>
</tr>
<tr>
<td>• Digital DVH data for all required critical normal structures, GTV, CTV, and PTVs for total dose plan</td>
<td></td>
</tr>
<tr>
<td>• All required structures MUST be labeled per the table in Section 6.5.</td>
<td></td>
</tr>
<tr>
<td>• Pancreas protocol CT scan (multi-detector CT scans, slice thickness &lt;2.5mm contrast enhanced using a bi-phasic technique) and/or MRI showing extent of tumor</td>
<td></td>
</tr>
<tr>
<td>• The “RTOG 1201 Datasheet” is available in the Forms section of the of the NRG Oncology/RTOG web site, <a href="http://www.rtog.org/ClinicalTrials/ProtocolTable/StudyDetails.aspx?study=1201">http://www.rtog.org/ClinicalTrials/ProtocolTable/StudyDetails.aspx?study=1201</a>. Submit via TRIAD with the digital data listed above.</td>
<td></td>
</tr>
<tr>
<td>Upon submission of the digital data via TRIAD, complete an online digital data transmission form (DDSI) located in the CORE LAB section on the NRG Oncology/RTOG web site at <a href="http://www.rtog.org/CoreLab/TRIAD.aspx">http://www.rtog.org/CoreLab/TRIAD.aspx</a></td>
<td></td>
</tr>
</tbody>
</table>

Note: All simulation and portal films and/or digital film images will be kept by the institution and only submitted if requested.

13.0 STATISTICAL CONSIDERATIONS
13.1 Primary Endpoint
13.1.1 Overall survival (OS) (failure: death due to any cause)

13.2 Secondary Endpoints (7/31/14)
13.2.1 Patterns of failure (local failure; metastatic failure)
13.2.2 Overall survival (OS) within SMAD 4 subsets
13.2.3 Adverse events
13.2.4 Correlation between SMAD4 status determined by IHC and genetic SMAD4 status

13.3 Randomization and Stratification (7/31/14)
Following the initial 3 cycles of gemcitabine and nab-Paclitaxel, patients who have not progressed will be randomized as described in Section 13.4.1. Patients will be stratified by CA19-9 status (< 1 vs. ≥ 1 to ≤ 90 vs. > 90) and SMAD4 status (intact vs. loss vs. undetermined) prior to randomization. The modified permuted block treatment allocation scheme described by Zelen (1974) will be used because it balances patient factors other than institution.

13.4 Sample Size Determination and Accrual (7/31/14)
13.4.1 Sample Size
This is a randomized Phase II trial comparing each of two chemoradiation treatments to a chemotherapy alone treatment. The goal of this trial is to determine if either or both of the
chemoradiation treatments provide a sufficient signal in overall survival to warrant pursuing a Phase III trial.

The sample size calculations are based on the primary hypothesis that a given chemoradiation treatment will show a signal for improved 2-year OS from 10% to 22.5% as compared to chemotherapy treatment alone. Following the initial 3 cycles of gemcitabine and nab-Paclitaxel, patients who have not progressed will be randomized to the following three arms in a 1:1:1 ratio:

- Gemcitabine and nab-Paclitaxel followed by intensified chemoradiation with concurrent capecitabine followed by gemcitabine and nab-Paclitaxel until progression (Arm 1)
- Gemcitabine and nab-Paclitaxel followed by standard chemoradiation with concurrent capecitabine followed by gemcitabine and nab-Paclitaxel until progression (Arm 2)
- Gemcitabine and nab-Paclitaxel until progression (Arm 3)

Each of the chemoradiation treatment arms will be compared to the chemotherapy alone arm. The required sample size for each comparison for the primary endpoint of OS is based on the following conditions:

- OS times are exponentially distributed with (at least approximately) constant hazards in both treatment arms
- The chemotherapy alone arm will have a 2-year OS of 10%
- The chemoradiation arm will have a 2-year OS of 22.5%
- Hazard ratio (chemoRT/chemo alone) = 0.65
- One-sided log-rank test at \( \alpha = 0.10 \)
- Statistical power of 90%
- 3 years of accrual with 1 year of follow-up
- One interim significance test for futility and a final test for efficacy

For each comparison, using the group sequential design method (Pocock 1977) with 1 interim analysis, 140 OS events are required to detect a signal for an increase in 2-year OS from 10% to 22.5%, translating into a hazard ratio (chemoRT/chemo alone) of 0.65. Given the conditions above, 86 patients per treatment arm will be required to be accrued uniformly over 3 years with an additional 1 year of follow-up. Guarding against an eligibility or lack-of-data rate of up to 10%, a total of 288 patients will be randomized. It is projected that there will be up to a 20% dropout rate (i.e., not being randomized) due to the development of systemic metastases after completion of 3 cycles of gemcitabine + nab-Paclitaxel. Given that, it is projected that 346 patients will need to be entered to reach the required number of randomized patients.

### 13.4.2 Accrual

Patient accrual is projected to be 8 cases per month randomized to the 3 treatment arms, with a ramp-up period in the first 6 months. The expected monthly accrual in months 1-3 and months 4-6 following activation are 0 and 1, respectively. If the total accrual during months 13 through 18 of the study is ≤ 20% of the targeted accrual (< 10 cases in total), then the protocol will be assessed for feasibility of completing accrual in a timely fashion.

### 13.4.3 Power Calculations for Secondary Endpoints

SMAD4 status will be assessed and used as a stratification factor. It is projected that there will be a 30%, 30%, and 40% distribution between the SMAD4 intact, loss, and undetermined groups respectively. This corresponds to 77 SMAD4 intact patients and 77 SMAD4 loss patients, each randomized across the 3 treatment arms.

To investigate the impact of the chemoradiation regimens within the SMAD4 intact subset, based on the above projections there will be ~25 SMAD4 intact patients randomized to each of the chemotherapy alone arm (Arm 3) and the intensified and standard chemoradiation arms (Arms 1 and 2). This sample size will provide 55% and 63% power to detect an increase in 2-year OS from 10% to 22.5% or 25%, respectively.
13.5 Analysis Plan (7/31/14)
13.5.1 Statistical Methods
Overall survival (OS) will be estimated by the Kaplan-Meier method (1958). For each comparison of a chemoradiation arm to the chemotherapy alone arm, the distribution of OS estimated between the two arms will be compared using the log rank test (Mantel 1966). The Cox proportional hazard regression model will be used to analyze the effects of factors, in addition to treatment, that may be associated with OS. Local and distant failure will be estimated by the cumulative incidence method (Kalbfleisch 1980) and the comparison of these endpoints between treatment arms will be done using Gray’s test (Gray 1988).

13.5.2 Routine Interim Reporting
Interim reports with statistical analyses are prepared every six months until the primary endpoint results have been presented. In general, the interim reports will contain information about:

- the patient accrual rate, including projected completion date (while accruing)
- institutional accrual
- distributions of important pretreatment and prognostic baseline variables
- the frequency and severity of adverse events due to protocol therapy
- compliance rates of treatment delivery with respect to the protocol prescription

The interim reports will not contain the results from the treatment comparisons with respect to the primary endpoint, OS, or any secondary endpoints, with the exception of reporting of adverse events.

13.5.3 Interim Analysis for Futility of Primary Endpoint: Overall Survival
For each comparison, there will be one interim significance test for futility of a treatment difference signal for improved OS. The timing of the interim analysis will be based on OS failure events (deaths), as described in Section 13.1. The maximum number of events required for each comparison is 140. The interim analysis for futility will occur at 50% of total events, or 70 deaths.

For each comparison, at the planned interim analysis, if the chemoradiation arm is not superior to the chemotherapy alone arm, as defined by a hazard ratio ($\lambda_{chemoRT}/\lambda_{chemo}$) ≥ 1, then accrual to the given chemoradiation treatment arm will be stopped (if applicable) and it will be reported that it cannot be concluded that there is a signal for improved OS with the given chemoradiation treatment arm. Otherwise, accrual to the given chemoradiation treatment arm or follow-up (as applicable) will continue until the final analysis. This provides 50% probability of concluding futility under the null hypothesis.

In addition to accrual, distributions of pretreatment characteristics, frequency and severity of adverse events and compliance with protocol treatment blinded efficacy results will be reported to the NRG Oncology DMC, following the required number of events for each planned interim analysis.

13.5.4 Data Monitoring Committee (DMC) Review
In addition to their review of the interim futility analysis as described in Section 13.5.3, the NRG Oncology DMC will meet to officially review this study twice per year for accrual (until accrual completed) and adverse events and on an “as needed” basis in between meetings.

13.5.5 CDUS Reporting
This study will be monitored by the Clinical Data Update System (CDUS) version 3.0. Cumulative CDUS data will be submitted quarterly by electronic means. Reports are due January 31, April 30, July 31, and October 31.

13.5.6 Analysis for Reporting the Initial Treatment Results
The primary hypotheses of this study are that (i) intensified radiochemotherapy, following gemcitabine and nab-Paclitaxel, (arm 1) will show a signal for improved 2-year OS from 10% to 22.5% as compared to chemotherapy alone (arm 3) and (ii) standard radiochemotherapy following gemcitabine and nab-Paclitaxel (arm 2) will show a signal for improved 2-year OS from 10% to 22.5% as compared to chemotherapy alone (arm 3), for patients with unresectable pancreas cancer. This major analysis will occur for each comparison after at least 140 OS failure events (deaths) have been observed within each comparison, unless the futility rules is satisfied for the given comparison. The usual components of the analysis are:
• tabulation of all cases entered and reasons for any patients excluded from the analysis
• institutional accrual
• patient accrual rate
• distribution of important pretreatment characteristics and prognostic baseline variables
• compliance rates of treatment delivery with respect to the protocol prescription
• observed results with respect to the primary and secondary endpoint

All eligible patients randomized will be included in each comparison and will be grouped by assigned treatment arm in the analysis. For each comparison, the primary hypothesis of signal for treatment benefit will be tested using the log-rank statistic with a significance level of 0.10, given that the futility boundary was not crossed per Section 13.5. Additional analyses of treatment effect will be performed using the Cox proportional hazard model with the stratification factors included as fixed covariates, as well as any factors that show an imbalance between the arms (e.g. age, gender, race, PS, etc.). Where feasible, treatment comparisons with respect to the primary endpoint (OS) will be compared within each ethnic and racial category.

13.6 Gender and Minorities (7/31/14)
Both men and women of all races and ethnic groups are eligible for this study. In conformance with the national Institutes of Health (NIH) Revitalization Act of 1993 with regard to inclusion of women and minorities in clinical research, possible interactions between race/ethnicity and treatment have been considered. Based on RTOG studies 0411 and 0020, it is projected that 52% of the patients will be men and 48% women; 8% will be of Hispanic or Latino ethnicity; racial distribution will be 79% white, 18% black or African American, and 3% across the other racial categories. Assuming no differences between the ethnicities, or among the races, the statistical power for detecting the hypothesized treatment difference in the randomized patients is 71% for males and 68% for females. The projected Hispanic/Latino and non-White accrual rates are too low for any meaningful treatment comparisons.

The following table lists the projected randomized accrual by gender, ethnic, and racial categories.

<table>
<thead>
<tr>
<th>Projected Distribution of Gender and Minorities</th>
<th>Gender</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Females</td>
</tr>
<tr>
<td><strong>Ethnic Category</strong></td>
<td></td>
</tr>
<tr>
<td>Hispanic or Latino</td>
<td>11</td>
</tr>
<tr>
<td>Not Hispanic or Latino</td>
<td>127</td>
</tr>
<tr>
<td><strong>Ethnic Category: Total of all subjects</strong></td>
<td>138</td>
</tr>
<tr>
<td><strong>Gender</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Racial Category</strong></td>
<td></td>
</tr>
<tr>
<td>American Indian or Alaskan Native</td>
<td>1</td>
</tr>
<tr>
<td>Asian</td>
<td>1</td>
</tr>
<tr>
<td>Black or African American</td>
<td>25</td>
</tr>
<tr>
<td>Native Hawaiian or other Pacific Islander</td>
<td>3</td>
</tr>
<tr>
<td>White</td>
<td>108</td>
</tr>
<tr>
<td><strong>Racial Category: Total of all subjects</strong></td>
<td>138</td>
</tr>
</tbody>
</table>
REFERENCES


Gray RJ. A class of K-samples test for comparing the cumulative incidence of a competing risk. *Ann Statistic*; **16**:1141-54

Hammel P, Huget F, Van Laethem JL, et al. Comparison of chemoradiotherapy (CRT) and chemotherapy (CT) in patients with a locally advanced pancreatic cancer (LAPC) controlled after 4 months of gemcitabine with or without erlotinib: Final results of the international phase III LAP 07 study. *J Clin Oncol* 31, 2013 (suppl; abstr LBA4003)


Mantel N. Evaluation of survival data and two new rank order statistics arising in its consideration. *Cancer Chemotherapy.*1966; Rep.50:163-70,


Pocock SJ. Group sequential methods in the design and analysis of clinical trials. *Biometrika*; 1977. 64:191-9


### STUDY PARAMETER TABLE: PRE-TREATMENT ASSESSMENTS

(See Sections 3.0 and 4.0 for additional details)

<table>
<thead>
<tr>
<th>Assessments</th>
<th>Time Points</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pre-Treatment assessments</td>
<td>≤ 30 days prior to step 1 registration</td>
</tr>
<tr>
<td>Pre-Treatment assessments</td>
<td>≤ 14 days prior to step 1 registration</td>
</tr>
<tr>
<td>Histological or Cytological confirmed diagnosis</td>
<td>Prior to step 1 registration</td>
</tr>
<tr>
<td>Submission of cell block or core tissue biopsy for determination of SMAD4 status by central laboratory</td>
<td>Must be submitted as soon as possible following step 1 registration.</td>
</tr>
<tr>
<td>History/physical with weight and vital signs</td>
<td>X</td>
</tr>
<tr>
<td>Performance status</td>
<td>X</td>
</tr>
<tr>
<td>CBC w/ diff &amp; ANC, platelets</td>
<td>X</td>
</tr>
<tr>
<td>Creatinine, ALT and AST, total bilirubin, alk phos,</td>
<td>X</td>
</tr>
<tr>
<td>Albumin, Na, K, Cl, Mg, CO₂</td>
<td>X</td>
</tr>
<tr>
<td>CA19-9</td>
<td>Baseline CA19-9</td>
</tr>
<tr>
<td>(in the event that a stent has been placed and biliary obstruction has been relieved, the CA19-9 should be drawn post stent placement)</td>
<td></td>
</tr>
<tr>
<td>Pancreas protocol CT/MRI</td>
<td>X</td>
</tr>
<tr>
<td>CT/MRI with IV contrast of abdomen/pelvis</td>
<td>Required only if whole-body FDG-PET is not obtained see Section 3.1</td>
</tr>
</tbody>
</table>

-continued on next page-
### APPENDIX I (7/31/14)

**STUDY PARAMETER TABLE: PRE-TREATMENT ASSESSMENTS (Continued)**

<table>
<thead>
<tr>
<th>Assessments</th>
<th>Time Points</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>≤ 30 days prior to step 1 registration</strong></td>
<td><strong>≤ 14 days prior to step 1 registration</strong></td>
</tr>
<tr>
<td>CT chest</td>
<td>Whole-body FDG-PET/CT may substitute for this test; see Section 3.1</td>
</tr>
<tr>
<td>Whole-body FDG-PET/CT</td>
<td>Chest CT and CT abd/pelvis may substitute for this test; see Section 3.1</td>
</tr>
<tr>
<td>Serum pregnancy test (if applicable)</td>
<td>X</td>
</tr>
<tr>
<td>Adverse event assessment</td>
<td>X</td>
</tr>
<tr>
<td>Biliary stent placement</td>
<td>For patients with biliary obstruction, see Section 4.1</td>
</tr>
<tr>
<td>Tissue for banking <em>(if patient consents)</em></td>
<td>Pre-treatment</td>
</tr>
<tr>
<td>Serum /Plasma for banking <em>(if patient consents)</em></td>
<td>Prior to start of step 1 chemotherapy</td>
</tr>
<tr>
<td>Whole blood for banking <em>(if patient consents)</em></td>
<td>Pre-treatment</td>
</tr>
<tr>
<td>Fine needle aspirate stained by routine cytopathology methods <em>(if patient consents)</em></td>
<td>Pre- treatment or at time of diagnostic biopsy</td>
</tr>
<tr>
<td>Fine needle aspirate unstained slide- ethanol fixed <em>(if patient consents)</em></td>
<td>Pre-treatment or at time of diagnostic biopsy</td>
</tr>
</tbody>
</table>
### APPENDIX I (7/31/14)

#### STUDY PARAMETER TABLE: ASSESSMENTS DURING TREATMENT

<table>
<thead>
<tr>
<th>Assessments</th>
<th>Time Points</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Weekly during Step 1 treatment (gem/nab-P), +/- 3 days (not required day 21)</td>
</tr>
<tr>
<td>History/physical with weight and vital signs</td>
<td>X</td>
</tr>
<tr>
<td>Performance status</td>
<td>X</td>
</tr>
<tr>
<td>CBC w/ diff &amp; ANC, platelets</td>
<td>X</td>
</tr>
<tr>
<td>Creatinine, ALT and AST, total bilirubin, alk phos,</td>
<td>X</td>
</tr>
<tr>
<td>CA19-9</td>
<td></td>
</tr>
<tr>
<td>Restaging CT/MRI of abdomen/pelvis</td>
<td></td>
</tr>
<tr>
<td>Treatment planning pancreas protocol CT or MRI (if CT contraindicated)</td>
<td></td>
</tr>
<tr>
<td>Adverse event evaluation</td>
<td>X</td>
</tr>
<tr>
<td>Serum /Plasma for banking (if patient consents)</td>
<td></td>
</tr>
</tbody>
</table>
### APPENDIX I

**STUDY PARAMETER TABLE: ASSESSMENTS DURING FOLLOW UP**

<table>
<thead>
<tr>
<th>Assessments</th>
<th>Time points</th>
</tr>
</thead>
<tbody>
<tr>
<td>Assessments Time Points</td>
<td>For Arms 1 and 2: 3-4 weeks after completion of chemoradiotherapy and then q 3 months until disease progression</td>
</tr>
<tr>
<td>Assessments Time Points</td>
<td>For Arm 3: 3-4 weeks after start of cycle 7, then q 3 months until disease progression</td>
</tr>
<tr>
<td>History/physical with weight and vital signs</td>
<td>X</td>
</tr>
<tr>
<td>Performance status</td>
<td>X</td>
</tr>
<tr>
<td>CBC w/ diff &amp; ANC, platelets</td>
<td>X</td>
</tr>
<tr>
<td>Creatinine, ALT and AST, total bilirubin , alk phos, Albumin</td>
<td>X</td>
</tr>
<tr>
<td>CA19-9</td>
<td>X</td>
</tr>
<tr>
<td>Pancreas protocol CT/MRI</td>
<td>Pancreas protocol CT (or MRI, if CT contraindicated) for determination of local control</td>
</tr>
<tr>
<td>CT/MRI with IV contrast of abdomen/pelvis</td>
<td>For determination of distant dissemination; pancreas protocol CT or MRI may substitute for this study if it includes the pelvis</td>
</tr>
<tr>
<td>CT chest</td>
<td>For determination of distant dissemination</td>
</tr>
<tr>
<td>Adverse event assessment</td>
<td>X</td>
</tr>
<tr>
<td>Serum/Plasma for banking (if patient consents)</td>
<td>21-42 days post chemoradiation completion (Arms 1 and 2) OR during cycle 6 of gem/nab-P chemotherapy (Arm 3)</td>
</tr>
</tbody>
</table>

### Assessments Time Points for Patients Who Come Off Study Treatment For Disease Progression:

- **Survival information** X
- **Performance status** X
- **Adverse event assessment** X

**Overall survival is to be reported to the NRG Statistics and Data Management Center q3 months.**
APPENDIX II

ZUBROD PERFORMANCE SCALE

<table>
<thead>
<tr>
<th>Score</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Fully active, able to carry on all predisease activities without restriction</td>
</tr>
<tr>
<td>1</td>
<td>Restricted in physically strenuous activity but ambulatory and able to carry work of a light or sedentary nature. For example, light housework, office work</td>
</tr>
<tr>
<td>2</td>
<td>Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours</td>
</tr>
<tr>
<td>3</td>
<td>Capable of only limited self-care, confined to bed or chair 50% or more of waking hours</td>
</tr>
<tr>
<td>4</td>
<td>Completely disabled. Cannot carry on self-care. Totally confined to bed</td>
</tr>
<tr>
<td>5</td>
<td>Death</td>
</tr>
</tbody>
</table>
APPENDIX III

AJCC STAGING SYSTEM

EXOCRINE AND ENDOCRINE PANCREAS

Primary Tumor (T)
TX Primary tumor cannot be assessed
T0 No evidence of primary tumor
Tis Carcinoma in situ*
T1 Tumor limited to the pancreas, 2 cm or less in greatest dimension
T2 Tumor limited to the pancreas, more than 2 cm in greatest dimension
T3 Tumor extends beyond the pancreas but without involvement of the celiac axis or the superior mesenteric artery
T4 Tumor involves the celiac axis or the superior mesenteric artery (unresectable primary tumor)
*This also includes the “PanInIII” classification.

Regional Lymph Nodes (N)
NX Regional lymph nodes cannot be assessed
N0 No regional lymph node metastasis
N1 Regional lymph node metastasis

Distant Metastasis (M)
M0 No distant metastasis
M1 Distant metastasis

Stage Grouping
Stage 0 Tis N0 M0
Stage IA T1 N0 M0
Stage IB T2 N0 M0
Stage IIA T3 N0 M0
Stage IIB T1 N1 M0
   T2 N1 M0
   T3 N1 M0
Stage III T4 Any N M0
Stage IV Any T Any N M1
APPENDIX IV

DUAL PHASE PANCREATIC IMAGING PROTOCOL

Dual phase pancreas CT protocol using iodinated intravenous contrast will be obtained at ≤ 2.5 mm slice pancreatic enhancement and during portal venous enhancement and will be obtained of the entire abdomen. If CT cannot be obtained because of allergy to iodinated contrast, gadolinium enhanced MRI will be utilized of the entire abdomen utilizing T1, T2 and dynamically obtained T1 weighted sequences at a slice thickness of maximally 7mm. If patient has history renal insufficiency or renal failure, and calculated GFR within 14 days prior to CT or MRI is < 30, noncontrast MRI will be utilized with T1 and T2 weighted sequences with a slice thickness not to exceed 7mm. If MRI cannot be obtained (i.e. implanted electronic devices), unenhanced ≤ 2.5 mm sections of the abdomen will be obtained by CT without intravenous contrast.

The timing of imaging after contrast administration: Bolus Tracking technique
The timing varies between the 16 and 64 detector scanners. For example, imaging of the entire abdomen during the pancreatic parenchymal phase, in a normal patient with normal cardiac circulation time, on a 16 would approximately begin at 36 seconds after the start of contrast injection and finish at 46 seconds. On the 64, it would begin at 40 seconds, and end at 45 seconds. (The pancreas is imaged during the same time period for both-- note both terminate at 45-46 seconds). The second phase is at 60 seconds after the start of injection depending on the scanner (60 for 16) in a normal patient.

A standard commercially available intravenous bolus tracking technique is recommended for use to control for variations in cardiac circulation time, to ensure that images are obtained during the correct phases of contrast enhancement. As is standard practice, a cursor is placed in the aorta at the level of the origin of the celiac axis and is used to detect when contrast arrives in the abdominal aorta and raises the density value to 100 Hounsfield Units. The 16 detector row scanner is instructed to begin scanning 16 seconds after that level is reached. Scanning of the abdomen is completed within 10 seconds, and after a subsequent 14 second delay, the abdomen is imaged again during the portal venous phase. In a normal patient, scanning of the abdomen during the first phase would begin 36 seconds after the start of contrast injection, and scanning of the second phase would begin 60 seconds after contrast injection.

In contrast, the 64 detector row scanner is instructed to begin 20 seconds after the 100 HU threshold is reached. Scanning of the abdomen is completed within 5 seconds, and after a subsequent delay of 15 seconds, the abdomen is imaged again during the portal venous phase. In a normal patient, scanning of the abdomen during the first phase would begin 40 seconds after the start of contrast injection, and scanning of the second phase would begin 60 seconds after contrast injection. The differences in timing between the 16 and 64 detector scanner are designed so that imaging of the pancreas during the first phase is finished at approximately 45-46 seconds after the start of contrast injection.
Resectability for the purpose of this clinical trial is based on the consensus statement published by Callery, et al.

**Unresectable tumors:**

- Major venous thrombosis of the portal vein or SMV extending for several centimeters (precluding vein resection and reconstruction).
- Encasement (>180°) of the SMA or, proximal hepatic artery.
- Abutment of the celiac trunk

**Tumors considered borderline resectable:**

- Venous involvement of the SMV/portal vein demonstrating tumor abutment with or without impingement and narrowing of the lumen, encasement of the SMV/portal vein but without encasement of the nearby arteries, or short segment venous occlusion resulting from either tumor thrombus or encasement but with suitable vessel proximal and distal to the area of vessel involvement, allowing for safe resection and reconstruction.
- Gastroduodenal artery encasement up to the hepatic artery with either short segment encasement or direct abutment of the hepatic artery, without extension to the celiac axis.
- Tumor abutment of the SMA not to exceed >180° of the circumference of the vessel wall.

**Tumors considered localized and resectable:**

- No radiographic evidence of SMV and portal vein abutment, distortion, tumor thrombus, or venous encasement.
- Clear fat planes around the celiac axis, hepatic artery, and SMA.
Shipping Instructions for Tissue Banking and Translational Research Samples:

- **U.S. Postal Service Mailing Address:** For Non-urgent FFPE or Non-frozen Specimens Only
  NRG Oncology Biospecimen Resource
  University of California San Francisco
  UCSF Box 1800
  2340 Sutter Street, Room S341
  San Francisco, CA 94143-1800

- **Courier Address (FedEx, UPS, etc.):** For Frozen or Trackable Specimens
  NRG Oncology Biospecimen Resource
  University of California San Francisco
  2340 Sutter Street, Room S341
  San Francisco, CA 94115

- Include all NRG Oncology paperwork in pocket of biohazard bag.
- Check that the Specimen Transmittal Form (ST) has the consent boxes checked off.
- Check that all samples are labeled with the NRG Oncology study and case number, and include date of collection as well as collection time point (e.g., pretreatment, post-treatment).

**FFPE Specimens:**
- Slides should be shipped in a plastic slide holder/slide box. Place a small wad of padding in top of the container. If you can hear the slides shaking it is likely that they will break during shipping.
- FFPE Blocks can be wrapped with paper towel, or placed in a cardboard box with padding. Do not wrap blocks with bubble wrap or gauze. Place padding in top of container so that if you shake the container the blocks are not shaking. If you can hear the block shaking it might break during shipping.
- Slides, Blocks, or Plugs can be shipped ambient or with a cold pack either by United States Postal Service (USPS) to the USPS address (94143) or by Courier to the Street Address (94115). **Do NOT ship on Dry Ice.**

**Frozen Specimens:**
- Multiple cases may be shipped in the same cooler, but make sure each one is in a separate bag and clearly identified. If possible keep Serum, Plasma, and Whole Bloods in separate bags.
- Place specimens and absorbent shipping material in Styrofoam cooler filled with dry ice (at least 7 lbs.). There should be plenty of dry ice under and above the specimens. If the volume of specimens is greater than the volume of dry ice then ship in a larger Styrofoam box, or two separate boxes. Any Styrofoam box can be used, as long as it is big enough.
- Specimens received thawed due to insufficient dry ice or shipping delays will be discarded and the site will be notified.
- Send frozen specimens on dry ice via overnight courier to the address above. Specimens should only be shipped Monday through Wednesday (Monday-Tuesday for Canada) to prevent thawing due to delivery delays. Saturday or holiday deliveries cannot be accepted. Samples can be stored frozen at -80°C until ready to ship.

For Questions regarding collection/shipping please contact the NRG Oncology Biospecimen Resource by e-mail: RTOG@ucsf.edu or phone: 415-476-7864 or Fax: 415-476-5271.
NRG Oncology FFPE SPECIMEN PLUG KIT INSTRUCTIONS

This Kit allows sub-sampling of an FFPE block for submission to the NRG Oncology Biospecimen Resource. The plug kit contains a shipping tube and a punch tool.

Step 1
If the block is stored cold, allow it to equilibrate for 30 minutes at room temperature. Place the punch tool on the paraffin block over the selected tumor area. (Ask a pathologist to select area with tumor.) Push the punch into the paraffin block. Twist the punch tool once around to separate the plug from the block. Then pull the punch tool out of the block. The punch should be filled with tissue sample.

Step 2
Label the punch tool with the proper specimen ID. DON'T remove specimen from the punch.

Step 3
Once punch tool is labeled, place in shipping tube and mail to address below. Please do not mix specimens in the same tube.

We will remove core specimen from the punch, embed in a paraffin block, and label with specimen ID. *NOTE: If your facility is uncomfortable obtaining the plug but wants to retain the tissue block, please send the entire block to the NRG Oncology Biospecimen Resource and we will sample a plug from the block and return the remaining block to your facility. Please indicate on the submission form the request to perform the plug procedure and return of the block.

Ship specimen plug kit, specimen in punch tool, and all paperwork to the address below. For Questions regarding collection/shipping or to order an FFPE Specimen Plug Kit, please contact the NRG Oncology Biospecimen Resource by e-mail: RTOG@ucsf.edu or call 415-476-RTOG(7864)/Fax 415-476-5271.

U.S. Postal Service Mailing Address: For Non-frozen, Non-urgent Specimens Only
NRG Oncology Biospecimen Resource
University of California San Francisco
UCSF Box 1800
2340 Sutter Street, Room S341
San Francisco, CA 94143-1800

Courier Address (FedEx, UPS, etc.): For ALL Frozen Specimens or Trackable shipments
NRG Oncology Biospecimen Resource
University of California San Francisco
2340 Sutter Street, Room S341
San Francisco, CA 94115
NRG Oncology BLOOD COLLECTION KIT INSTRUCTIONS

This Kit is for collection, processing, storage, and shipping of serum, plasma, or whole blood (as specified by the protocol):

**Kit contents:**
- One Red Top tube for serum (A)
- One Purple Top EDTA tube for plasma (B)
- One Purple Top EDTA tube for Whole Blood (C)
- Twenty-five (25) 1 ml cryovials
- Biohazard bags (3) and Absorbent shipping material (3)
- Styrofoam container (inner) and Cardboard shipping (outer) box
- UN1845 DRY Ice Sticker and UN3373 Biological Substance Category B Stickers
- Specimen Transmittal Form (ST) and Kit Instructions

**PREPARATION AND PROCESSING OF SERUM, PLASMA AND WHOLE BLOOD:**

**(A) Serum (if requested): Red Top Tube**
- Label as many 1ml cryovials (5 to 10) as necessary for the serum collected. Label them with the NRG Oncology study and case number, collection date, time, and time point, and clearly mark cryovials “serum”.

**Process:**
1. Allow one red top tube to clot for 30 minutes at room temperature.
2. Spin in a standard clinical centrifuge at ~2500 RPM for 10 minutes at 4°C (preferred). If sites are unable to process samples at 4°C then spinning at room temperature is acceptable if done within 2 hours of draw but must be noted on the ST.
3. Aliquot 0.5 ml serum into as many cryovials as are necessary for the serum collected (5 to 10) labeled with NRG Oncology study and case numbers, collection date/time, protocol time-point collected (e.g. pretreatment, post-treatment), and clearly mark specimen as “serum”.
4. Place cryovials into biohazard bag and immediately freeze at -70 to -90°C, and store frozen until ready to ship. See below for storage conditions.
5. Store serum at -70 to -90°C until ready to ship on dry ice. See below for storage conditions.

**PLEASE MAKE SURE THAT EVERY SPECIMEN IS LABELED and include collection time point on the ST.**

**(B) Plasma (if requested): Purple Top EDTA tube #1**
- Label as many 1ml cryovials (5 to 10) as necessary for the plasma collected. Label them with the RTOG study and case number, collection date, time, and time point, and clearly mark cryovials “plasma”.

**Process:**
1. After collection, invert tube(s) multiple times to ensure adequate mixing of EDTA.
2. Centrifuge specimen(s) within one hour of collection in a standard clinical centrifuge at ~2500 RPM for 10 minutes at 4°C (preferred). If sites are unable to process samples at 4°C then spinning at room temperature is acceptable if done within 2 hours of draw but must be noted on the ST.
3. If the interval between specimen collection and processing is anticipated to be more than one hour, keep specimen on ice until centrifuging is performed.
4. Carefully pipette and aliquot 0.5 ml plasma into as many cryovials as are necessary for the plasma collected (5 to 10) labeled with RTOG study and case numbers, collection date/time, time point collected and clearly mark specimen as “plasma”. Avoid pipetting up the buffy coat layer.
5. Place cryovials into biohazard bag and immediately freeze at -70 to -90°C.
6. Store frozen plasma until ready to ship on dry ice.
7. See below for storage conditions.
PLEASE MAKE SURE THAT EVERY SPECIMEN IS LABELED and include collection time point on the ST.

NRG Oncology BLOOD COLLECTION KIT INSTRUCTIONS (continued)

(C) Whole Blood for DNA (if requested): Purple Top EDTA tube #2
- Label as many 1ml cryovials (3 to 5) as necessary for the whole blood collected. Label them with the NRG Oncology study and case number, collection date/time, and time point, and clearly mark cryovials “blood”.

Process:
1. After collection, invert tube(s) multiple times to ensure adequate mixing of EDTA. Blood can also be mixed for 5 minutes on a mixer at room temperature.
2. Carefully pipette and aliquot 1.0 ml blood into as many cryovials as are necessary for the blood collected (3 to 5) labeled with NRG Oncology study and case numbers, collection date/time, time point collected and clearly mark specimen as “blood”.
3. Place cryovials into biohazard bag and freeze immediately at -70 to -80°C.
4. Store blood samples frozen until ready to ship on dry ice.
5. See below for storage conditions.

PLEASE MAKE SURE THAT EVERY SPECIMEN IS LABELED and include collection time point on ST.

Freezing and Storage:
- Freeze Blood samples in a -80°C Freezer or on Dry Ice or snap freeze in liquid nitrogen.
- Store at -80°C (-70°C to -90°C) until ready to ship.
  - If a -80°C Freezer is not available,
    - Samples can be stored short term in a -20°C freezer (non-frost free preferred) for up to one week (please ship out Monday-Wednesday only; Canada: Monday-Tuesday only).
  OR:
    - Samples can be stored in plenty of dry ice for up to one week, replenishing daily (please ship out on Monday-Wednesday only; Canada: Monday-Tuesday only).
  OR:
    - Samples can be stored in liquid nitrogen vapor phase (ship out Monday-Wednesday only; Canada: Monday-Tuesday only).
- Please indicate on Specimen Transmittal Form the storage conditions used and time stored.

Shipping/Mailing:
- Ship specimens on Dry Ice overnight Monday-Wednesday (Monday-Tuesday from Canada) to prevent thawing due to delivery delays. Saturday and holiday deliveries cannot be accepted.
- Include all NRG Oncology paperwork in a sealed plastic bag and tape to the outside top of the Styrofoam box.
Wrap frozen specimens of same type (i.e., all serum together, plasma together and whole bloods together) in absorbent shipping material and place each specimen type in a separate biohazard bag. Place specimen bags into the Styrofoam cooler and fill with plenty of dry ice (7-10 lbs/3.5kg minimum). Add padding to avoid the dry ice from breaking the tubes.

Place Styrofoam coolers into outer cardboard box, and attach shipping label and UN3373 and UN1895 stickers to outer cardboard box.

Multiple cases may be shipped in the same cooler, but make sure each one is in a separate bag and that there is enough room for plenty of dry ice. Add padding to avoid the dry ice from breaking the tubes.

For questions regarding collection, shipping or to order a Blood Collection Kit, please e-mail RTOG@ucsf.edu or call (415)476-7864.

Shipping Address:
Courier Address (FedEx, UPS, etc.): For all Frozen Specimens
NRG Oncology Biospecimen Resource
University of California San Francisco
2340 Sutter Street, Room S341
San Francisco, CA 94115
For questions, call 415-476-7864 or e-mail: RTOG@ucsf.edu