A PHASE II PILOT TRIAL OF NIVOLUMAB + ALBUMIN-BOUND PACLITAXEL + PARICALCITOL + CISPLATIN + GEMCITABINE (NAPPCG) IN PATIENTS WITH PREVIOUSLY UNTREATED METASTATIC PANCREATIC DUCTAL ADENOCARCINOMA

IND Exempt

SPONSOR

HonorHealth

10510 North 92nd Street, Scottsdale, AZ, 85258 (via partial support from both the TGen Foundation and from Bristol Myers Squibb (BMS protocol CA209-385) to HonorHealth)

VERSION DATE

Amendment 6, Version 7.0, 15Jul2020

Protocol Amendment History
Amendment 5, Version 6.0, 13 September 2019
Amendment 4, Version 5.0, 06 July 2018
Amendment 3, Version 4.0, 31 March 2017
Amendment 2, Version 3.0, 25 September 2016
Amendment 1, Version 2.0, 09 May 2016
Original Protocol, Version 1.0, 11 January 2016

Lead Principal Investigator HonorHealth Site Principal Investigator Erkut Borazanci, MD, MS HonorHealth Research Institute 10510 N. 92nd Street Scottsdale, AZ 85258 Tel: 480-323-1350 Fax: 480-323-1359 Email: Erkut.Borazanci@honorhealth.com	Special Consultant Daniel D. Von Hoff, MD, FACP Chief Scientific Officer HonorHealth Research Institute Physician in Chief, Distinguished Professor Translational Genomics Research Institute (TGen) 10510 N. 92nd Street Scottsdale, AZ 85258 Tel: 480-323-1350 Fax: 480-323-1359 Email: dvh@tgen.org
Sub-Investigator Gayle S. Jameson, MSN, ACNP-BC, AOCN Honor Health Research Institute 10510 N. 92nd Street Scottsdale, AZ 85258 Tel: 480-323-1350 Fax: 480-323-1359 Email: gayle.jameson@honorhealth.com	Sub-Investigator Ron Korn, MD, PhD Scottsdale Medical Imaging, LTD PO Box 1573 Scottsdale, AZ 85252 Tel: 480-425-5000 Fax: 480-425-5033 Email: rkorn@imagingendpoints.com
Sub-Investigator Lana Caldwell, RN, MSN Honor Health Research Institute 10510 N. 92nd Street Scottsdale, AZ, 85258	Sub-Investigator Karen L. Ansaldo, PharmD, BCPS Honor Health Research Institute Pharmacy 10460 N. 92nd Street

Tel: 480-323-1074 Fax: 480-323-1359 Email: lana.caldwell@honorhealth.com	Scottsdale, AZ, 85258 Tel: 480-323-1019 Fax: 480-323-1059 Email: karen.ansaldo@honorhealth.com

SOURCE OF SUPPORT

This study is partially funded by

Bristol-Myers Squibb

AND

TGen

Foundation

CONFIDENTIAL

INVESTIGATOR'S PROTOCOL AGREEMENT

Protocol No.: **NAPPCG-EB 2015-001**

Version 7.0, May 2020

I confirm that my staff and I have carefully read and understand this protocol. I/we agree to comply with the procedures and terms of the study specified herein. In particular, I/we have agreed to:

- Abide by all obligations stated on Form FDA 1572 and on other document(s) required by local regulatory authority.
- Retain records and documents related to this Trial for at least 7 years after the last approval of a marketing application in an International Conference on Harmonization (ICH) region and until there are no pending or contemplated marketing applications in an ICH region or at least 7 years have elapsed since the formal discontinuation of clinical development of the investigational products.
- Comply with Good Clinical Practice (GCP) and all applicable regulatory requirements.
- Maintain confidentiality and assure security of HonorHealth confidential documents.
- Obtain Institutional Review Board (IRB) approval of the protocol, any amendments to the protocol, and periodic re-approval as required, and to keep the IRB informed of adverse events and periodically report the status of the study to them.
- Not implement any deviations from or changes to the protocol without agreement from the Lead Sponsor-Investigator and HonorHealth and prior review and written approval from the IRB, except where necessary to eliminate an immediate hazard to the patients or for administrative aspects of the study (where permitted by all applicable regulatory requirements).
- Assure that each patient enrolled into the Trial has read, understands, and has signed the Informed Consent.
- Ensure that I and all persons assisting me with the study are adequately informed and trained about the investigational drug and of their study-related duties and functions as described in the protocol.
- Make prompt reports of serious adverse events (SAEs) and deaths (within 1 business day of learning of the death and 2 business days of learning of the SAE) to HonorHealth.
- Assure access by HonorHealth monitors, and/or FDA to original source documents.
- Prepare and maintain adequate and accurate case histories designed to record all observations and other data pertinent to the investigation on each individual treated in the investigation.
- Arrange for the transfer of appropriate data from case histories to case report forms for the collection and transmission of data to HonorHealth.
- Cooperate fully with any study-related GCP audit as performed by HonorHealth quality assurance group.
- Abide by the stipulations in the Disclosure of Data section and the manuscript preparation/authorship guidelines established at the outset of the study.

Investigator's Printed Name: _____

Investigator's Signature: _____ Date: _____

SAE REPORTING

All SAEs must be reported promptly to HonorHealth after the Investigator recognizes/ classifies the event as a SAE. For life-threatening or fatal events, the Investigator must report initial information on the SAE **within 1 business day** of becoming aware of the event, preferably by fax or alternatively by phone or email.

HonorHealth Drug Safety Team

24 Hour Phone #: 480-323-1350

Fax # : 480-323-1560

Email: DrugSafety@honorhealth.com

Protocol Schema

Patient with metastatic pancreatic cancer previously untreated for their metastatic disease

⇩

Signed informed consent

⇩

If protocol eligible

⇩

Cycles 1-4 and beyond if not on maintenance therapy

A cycle is defined as 6 weeks (42 days) with the following treatment schedule

- Nivolumab – 240 mg as a 60 minute infusion on days 1, 15, 29
- Albumin-bound paclitaxel – 125 mg/m^2 over 30 minutes IV infusion on days 1, 8 and 22, 29
- Cisplatin* – 25 mg/m^2 over 60 minutes IV infusion on days 1, 8 and 22, 29
- Gemcitabine – 1000 mg/m^2 over 30 minutes IV infusion on days 1, 8 and 22, 29
- Paricalcitol – 25 micrograms IV on days 1,4,8,12,15,18,22,26,29,32,36,39 (+/-1 day allowed for dosing

*Please see details in protocol for hydration and supportive care items

TABLE OF CONTENTS

14 TABLES

1 BACKGROUND AND RATIONALE

1.1 Background

Despite decades of basic and clinical research, effective therapy for the treatment of patients with pancreatic ductal adenocarcinoma (PDAC) remains one of the greatest unmet clinical needs in oncology today. Currently, PDAC accounts for approximately 7% of all cancer-related mortality and has the lowest 5-year survival rate among all cancer types in the United States (Siegel et al, 2015). PDAC is currently the 4th leading cause of death from cancer in the U.S. with estimates in 2015 for 48,960 people diagnosed and 40,560 dying from the disease (Siegel et al, 2015). Worldwide it will claim more than 300,000 lives this year (Torre et al, 2015). It is projected that by 2030, pancreatic cancer will become the second leading cause of cancer-related death in the US (Rahib et al, 2014). Improved strategies for early detection and for treatment of PDAC are desperately needed. Additionally, further investigation into patient-reported quality of life and pain levels in this population needs to be explored.

For patients with advanced disease, the regimen of 5-fluorouracil/ leucovorin/ irinotecan/ oxaliplatin (FOLFIRINOX) compared with gemcitabine demonstrated improvement in both progression-free survival (6.4 vs. 3.3 months) and overall survival (11.1 vs. 6.8 months) for patients with a good performance status. FOLFIRINOX is often associated with substantial grade 3 and 4 toxicities, including diarrhea, nausea, vomiting, fatigue, neutropenia and febrile neutropenia, and cannot be given to patients > 76 years of age or in some cases to patients with head of the pancreas tumors (Conroy 2011, Assaf 2011).

Von Hoff and colleagues (2011) presented phase I/II data supporting the use of albumin-bound paclitaxel and gemcitabine in a phase I/II trial in patients with previously untreated advanced PDA. All patients at the recommended phase II dose (n=44) had a decrease in CA 19-9. This regimen also demonstrated an objective response rate of 48% with median survival of 12.2 months and 48% 1-year survival and 25% 2-year survival.

An international phase III trial comparing the albumin-bound paclitaxel plus gemcitabine combination to gemcitabine single agent was conducted. In that study published in 2013 (Von Hoff et al), a total of 861 patients were randomly assigned to albumin-bound paclitaxel plus gemcitabine (431 patients) or gemcitabine (430). The median overall survival was 8.5 months in the albumin-bound paclitaxel plus gemcitabine group as compared to 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 albumin-bound paclitaxel plus 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 albumin-bound paclitaxel-gemcitabine group versus 3.7 months the gemcitabine alone arm (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 albumin-bound paclitaxel-gemcitabine group vs. 27% in the gemcitabine group), fatigue (17% vs. 7%) and neuropathy (17% vs. 1%). Febrile neutropenia occured in 3% versus 1% of the patients in the two groups respectively. In the albumin-bound paclitaxel plus gemcitabine group, neuropathy of grade 3 or higher improved to grade 1 or lower in a median of 29 days.

The conclusion from that study was in patients with metastatic pancreatic adenocarcinoma, albumin-bound paclitaxel plus gemcitabine significantly improved overall survival, progression

free survival, and response rate, but rates of peripheral neuropathy and myelosuppression were increased. (funded by Celgene; ClinicalTrials.gov number NCT00844649)

In a very recent long term follow up on the study (Goldstein et al, 2015), the median overall survival was significantly longer for albumin-bound paclitaxel + gemcitabine versus gemcitabine alone (8.7 versus 6.6 months; hazard ratio = 0.72;95% confidence interval (CI) = 0.62 to 0.83, P<0.001. Long term (> than three years) survivors were indentified in the albumin-bound paclitaxel plus gemcitabine arm (4%). There were no survivors in the single agent gemcitabine arm.

1.2 Rationale

The NAPPCG regimen proposed in this protocol is built on the rationale outlined in Table 1. Building on the design and mechanisms of action of the albumin-bound paclitaxel plus gemcitabine combination, we recently introduced a third cytotoxic agent, cisplatin, to be added to this doublet. The rationale for adding cisplatin to albumin-bound paclitaxel and gemcitabine is that in a study of 1,029 patients whose pancreatic cancer tumors were sent for molecular profiling, 57% of these tumors were negative for ERCC1, indicating potential sensitivity to a platinum anti-tumor agent (Von Hoff, 2012). In addition to the above, in our whole genome/transcriptome sequencing analysis, we found that abnormal repair pathways were a feature of all of the pancreatic cancers that were sequenced (Liang 2012). Cisplatin prevents cellular DNA repair by binding to and causing crosslinking of DNA, triggering apoptosis. Cisplatin has been used in other combination regimens to treat patients with PDAC. For example, the cisplatin, epirubicin, 5-fluorouracil and gemcitabine (PEFG) regimen had an acceptable toxicity profile and was associated with a 24% partial response rate, 5 month progression-free survival (PFS) and 8.3 month overall survival as second line therapy (Reni et al, 2008).

Prior to 2015, there were no documented reports of the combination of cisplatin with albumin-bound paclitaxel and gemcitabine in the treatment of any human cancer. However, cisplatin had been combined with paclitaxel and gemcitabine in the treatment of patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) patients and had shown substantial antitumor activity with an acceptable safety profile. In that phase I-II study of 65 patients with advanced NSCLC, the overall response rate was 57% (Frasci et al, 1999).
More recently there has been even more compelling science indicating that one should consider DNA repair as an Achilles heel in pancreatic cancer (Evers et al, 2014) A team led by Nurse Practitioner Gayle Jameson (Jameson et al, 2015) recently reported on the phase Ib/II trial of the combination of nanoparticle paclitaxel (now called albumin-bound paclitaxel) plus gemcitabine plus cisplatin. In the first 10 patients with stage IV pancreatic cancer they reported 20% Complete response (CR), 60% Partial response (PR), 10% stable disease, 10% progressing on the trial. The trial is ongoing but is obviously very promising with an acceptable toxicity profile and complete responses (CR) .

Most recently the spectacular work of Sherman et al (2015) has awakened the world of pancreatic cancer research to the possibility that Vitamin D could be a substantial player in normalizing the tumor microenvironment from an immunologically friendly (to the tumor) one to an immunologically hostile one (e.g. decreased IL6, decreased CXCL12 etc.). In addition, the vitamin D analog decreased production of collagen, decreased Myeloid derived Suppressor cell (MDSC) and decreased regulating T cells. This work is begging to be looked at in a clinical situation and promises to turn around the problem that basically for patients with PDAC, there

has never been a substantial response to anti-immune blockade agents (Le et al, 2013; Royal et al, 2010).

Based on the very promising clinical data with albumin-bound paclitaxel plus gemcitabine plus cisplatin plus the substantial modulation of the immune environment produced by albumin-bound paclitaxel plus gemcitabine plus paricalcitol (the synthetic Vitamin D) with infiltration of CD3 positive lymphocytes in an ongoing neoadjuvant trial (unpublished SU2C data courtesy of Drs. O'Dwyer and Drebin University of Pennsylvania), we are now in a position to put together an ultimate attack against the disease. It is based on the above that we plan this bold approach of combining immuno-oncology into a reengineered (normalized) microenvironment to look for a dramatic effect in patients with advanced pancreatic cancer.

Table 1 Regimen Rationale

Agent	Rationale	Reference
Nivolumab	• Presence of PD1	Nomi et al, 2007 Gattalica et al, 2014
Gemcitabine	• Improved survival as single agent and in combination	Burris et al, 1997 Von Hoff et al, 2011, 2013
Albumin-bound Paclitaxel	• Active as a single agent against pancreatic cancer • Improved survival in combination with Gemcitabine • Decreases tumor stroma by decreasing cancer associated fibroblasts with improving elasticity • In combination allows penetration of lymphocytes	Peddi et al, 2013 Von Hoff et al, 2013 Alvarez et al, 2013
Paricalcitol	• Acts to reengineer the tumor stroma decrease collagen and decrease IL6 plus CXCL12	Sherman et al, 2014
Cisplatin	• DNA repair abnormalities in patients with cancer	Von Hoff et al, 2012 Liang et al, 2012

Please note that to date there is not a great deal of information on the use of nivolumab with conventional chemotherapies. What is known is that for combinations of nivolumab (maximum dose used 10 mg/kg) with gemcitabine/cisplatin, with pemetrexed/cisplatin or with carboplatin/paclitaxel that there were no dose limiting toxicities noted (nivolumab Investigator Brochure version No. 14, 30June2015).

As of July 6, 2018, there have been 25 patients enrolled on the current protocol (NCT02754726) with the first 10 patient outcomes presented at the Gastrointestinal Cancer Symposium [Borazanci et al 2018]. In the first 10 patients that was presented, the overall response rate is 80% with 8/10 patients attaining a PR. In unpublished data from the 25 patients the response rate remains above 80%, all partial responses

1.3 Indications and Adverse Reactions of Nivolumab (Taken from Prescribing

Information/Package Insert for Opdivo®)

See Appendix E for links to current prescribing information

1.3.1 Adverse Reactions

Most common adverse reactions (>20%) in patients were: fatigue, rash, musculoskeletal pain, pruritis, diarrhea, nausea, asthesia, cough, dyspnea, constipation, decreased appetite, back pain, arthralgia, upper respiratory tract infection, pyrexia.

See Appendix G for Management Algorithms for Adverse Events Related to Nivolumab Therapy.

1.4 Potential Risks of Albumin-bound Paclitaxel (formerly known as nab-paclitaxel)

The most common toxicities reported for albumin-bound paclitaxel include myelosuppression, predominantly neutropenia, infections (24%), dyspnea (12%), peripheral neuropathy and nausea and vomiting, myalgias and arthralgias, mucositis, alopecia, transaminitis, serum creatinine elevation. Other reported infrequent toxicities include: allergic reaction, loss of appetite, diarrhea, constipation, cough, edema, fever, pruitis, hypotension, nail changes, vision changes, rash, pulmonary edema, irregular heartbeat (see Appendix E for link to prescribing information).

1.4.1 Side Effects

- Hematologic disorders – Neutropenia was dose dependant and reversible. Among patients with metastatic breast cancer in the randomized trial, neutrophil counts declined below 500 cells/mm^3 (grade 4) in 9% of the patients treated with a dose of 260 mg/m^2 compared to 22% in patients receiving paclitaxel injection at a dose of 175 mg/m^2.

- Infections – Infectious episodes were reported in 24% of the patients treated with paclitaxel. Oral candidiasis, respiratory tract infections and pneumonia were the most frequently reported infectious complications.Pancytopenia has been observed in clinical trials.

- Hypersensitivity reactions (HSRs) – Grade 1 or 2 HSRs occured on the day of paclitaxel administration and consisted of dyspnea (1%) and flushing, hypotension, chest pain and arrhythmia (all < 1%). The use of paclitaxel in patients previously exhibiting hypersensitivity to paclitaxel injection or human albumin has not been studied.

- Cardiovascular – Hypotension, during the 30-minute infusion, occured in 5% of patients. Bradycardia, during the 30-minute infusion, occurred in <1% of patients. These vital sign changes most often caused no symptoms and required neither specific therapy nor treatment discontinuation. Severe cardiovascular events possibly related to single-agent paclitaxel occurred in approximately 3% of patients. These events included cardiac ischemia/infarction, chest pain, cardiac arrest, supraventricular tachycardia, edema, thrombosis, pulmonary

thromboembolism, pulmonary emboili, and hypertension. Cases of cerebrovascular attacks (strokes) and transient ischemic attacks have been reported. Electrocardiogram (ECG) abnormalities were common among patients at baseline. ECG abnormalities on study did not usually result in symptoms, were not dose-limiting, and required no intervention. ECG abnormalities were noted in 60% of some patients.

1.5 Potential Risks of Cisplatin

The most common toxicities of cisplatin include nephrotoxicity (28-36%; acute renal failure and chronic renal insufficiency), peripheral neuropathy (dose and duration dependent), nausea and vomiting (76% to 100%), myelosuppression (25% to 30%; nadir: day 18-23; recovery: by day 39; mild with moderate doses, mild-to-moderate with high-dose therapy), liver enzymes increased (especially SGOT and bilirubin), ototoxicity (10% to 30%; manifested as high frequency hearing loss; ototoxicity is especially pronounced in children) and tissue irritation (extravasation).

Other toxicities (<1%) include alopecia (mild), anaphylactic reaction, arrhythmias, arterial vasospasm (acute), blurred vision, bradycardia, diarrhea, heart block, heart failure, hemolytic anemia (acute), hemolytic uremic syndrome, hypercholesterolemia, hypocalcemia, hypokalemia, hypomagnesemia, hyponatremia, hypophosphatemia, limb ischemia (acute), mesenteric ischemia (acute), myocardial infarction, myocardial ischemia, mouth sores, neutropenic typhlitis, optic neuritis, orthostatic hypotension, pancreatitis, papilledema, phlebitis, reversible posterior leukoencephalopathy syndrome (RPLS), Syndrome of Inappropriate antidiuretic hormone secretion (SIADH), stroke, thrombophlebitis and thrombotic thrombocytopenic purpura (see Appendix E for link to prescribing information).

1.6 Potential Risks of Gemcitabine

The most common toxicities reported for gemcitabine include myelosuppression, transient elevations in serum transaminases (approximately 70%), nausea and vomiting (69%), fever (41%), rash (30%), diarrhea (19%), flu syndrome, (19%), infection (16%), alopecia (15%), edema (13%), stomatitis (11%),) neurotoxicity (mild 10%, severe <1%), mild proteinuria and hematuria; Hemolytic Uremia Syndrome (HUS) reported rarely (0.25%), dyspnea (0.2%) and serious pulmonary toxicity (0.06%). Also reported include constipation and pruritus (see Appendix E for link to prescribing information).

1.7 Potential Risks of Paricalcitol

Paricalcitol [19-nor-1α, 25 – dihydroxyvitamin D2] (also known as Zemplar) is a vitamin D analog of calcitriol with modifications to the side chain (D2) and the A (19-nor) ring. We have selected paricalcitol as our Vitamin D analog based on its broad use over a decade in the management of calcium and Vitamin D homeostasis in patients undergoing renal dialysis and because it is being used in an ongoing neoadjuvant clincial trial with albumin-bound paclitaxel + gemcitabine (PI - Peter O'Dwyer) with good safety in the first 15 patients. Paricalcitol is chemically designated as 19-nor-12,B (3),25-trihydroxy-9,10-secoergosta5(Z), 7 (E), 22 (E)–triene, and is a non-metabolized vitamin D analogue that has little hypercalcemic activity (see Appendix I for package insert). As such, it is the ideal compound to effect the desired transcriptional change in the tumor microenvironment (Sherman et al, 2014). In addition to well-established effects on bone mineral homeostasis, there is increasing recognition that vitamin D

may play a role in renal and cardiovascular function, as well as T Cell function in some circumstances. Randomized clinical trials showed a positive effect of paricalcitol in patients with chronic renal disease on mineral metabolism, on cardiovascular outcome, and on markers of kidney damage (Bellasi et al, 2013). This positive effect on survival is observed not only in patients with elevated intact parathyroid hormone (iPTH), but even in those with low levels of this hormone (Ozzolino et al, 2012). The recommended starting dose of paricalcitol is 0.04 micrograms/kg (or about 3 micrograms per dose), but total weekly doses of 15 to 30 micrograms are reported in the literature without safety concerns (Izanuerdo et al, 2012, Kettler et al, 2012, Tanblul et al, 2012). A trial in combination with taxol in breast cancer patients gave up to 7 micrograms per day for 12 weeks (Lawrence et al, 2013).

There have been trials of paricalcitol in cancer patients also; In a population of prostate cancer patients (mean age 74) thrice weekly paricalcitol was administered at doses up to 25 micrograms, with no dose-limiting toxicity (Schwartz et al, 2005). The authors suggested that higher doses could be explored. However, we do not feel higher doses are needed in this trial, since all patients in their study showed a decline in iPTH, with minimal toxicity. There was mild nausea in 8/18 patients, mild vomiting in 2/18 patients, and a photosensitive rash in 1/ 18. Four patients developed hypercalcemia, only one higher than 12 mg/dl (and this only 14.3 mg/dl) (Schwartz et al, 2005). Accordingly we propose to use a two times weekly IV schedule (given concerns regarding oral absorption in pancreatic cancer patients) at a flat dose of 25 micrograms. A detailed population pharmacokinetic analysis including over 600 patients showed mean plasma clearance of 1.75l/h, and stable phosphorus and calcium levels in the first 30 days of treatment (Nortersheusen et al, 2012). This analysis lends support to both the dose and schedule chosen for our NAPPCG regimen, as well as lends support to the schedule of weekly electrolyte monitoring.

1.7.1 Potential Risks

- Gastrointestinal Disorders: abdominal discomfort, constipation, diarrhea, nausea, vomiting, dysphagia, gastritis, intestinal ischemia, rectal hemorrhage, gastrointestinal hemorrhage, aspartate aminotransferase increased

- General Disorders and Administration Site Conditions: asthenia, chest discomfort, chest pain, peripheral edema, fatigue, feeling abnormal, gait disturbance, injection site extravasation, injection site pain, pain, swelling, thirst, chills, fever

- Infections and Infestations: nasopharyngitis, upper respiratory tract infection, vaginal infection, influenza, pneumonia, sepsis

- Metabolism and Nutrition Disorders: decreased appetite, hypercalcemia, hyperkalemia, hyperphosphatemia, hypocalcemia, weight decreased

- Musculoskeletal and Connective Tissue Disorders: joint stiffness, muscle twitching, myalgia, arthralgia

- Neoplasms Benign, Malignant and Unspecified: breast cancer

- Nervous System Disorders: cerebrovascular accident, dizziness, dysgeusia, headache, hypoesthesia, myoclonus, paresthesia, syncope, unresponsive to stimuli

- Psychiatric Disorders: agitation, confusional state, delirium, insomnia, nervousness, restlessness
- Reproductive System and Breast Disorders: breast pain, erectile dysfunction
- Respiratory, Thoracic and Mediastinal Disorders: cough, dyspnea, orthopnea, pulmonary edema, wheezing
- Skin and Subcutaneous Tissue Disorders: alopecia, blister, hirsuitism, night sweats, rash (pruritic), pruritus, skin burning sensation, urticaria
- Vascular Disorders: hypertension, hypotension, angioedema
- Other: dry mouth

(See Appendix E for link to prescribing information).

1.8 Potential Risks of Albumin-bound Paclitaxel + Gemcitabine

The safety of albumin-bound paclitaxel plus gemcitabine was reported by Von Hoff and colleagues (Von Hoff 2011, 2013). The most common toxicities seen in the phase III trial were anemia, leukopenia, neutropenia, thrombocytopenia, fatigue, alopecia, sensory neuropathy and nausea.

1.9 Potential Risks of Albumin-bound Paclitaxel, + Cisplatin, + Gemcitabine

The combination of albumin-bound paclitaxel, cisplatin, and gemcitabine has just been recently reported in a preliminary manner (Jameson et al, 2015). In the report on the first 10 patients on that phase Ib/II trial overall grade 3 toxicities included anemia (30%); diarrhea (20%); C-difficile colitis (10%); hypoglycemia (10%); lung infection (20%); decreased lymphocyte count (10%);increased lymphocyte count (10%); nausea (10%); neutropenia (30%); peripheral motor neuropathy (10%); thrombocytopenia (50%); vomiting (10%). Grade 4 toxicities included febrile neutropenia 10%); thrombocytopenia (50%); and sepsis (10%). The study is being expanded at the cisplatin dose of 25mg/m^2.

1.10 Potential Risks of Nivolumab + Albumin-bound Paclitaxel + Paricalcitol + Cisplatin + Gemcitabine

Since this will be the first time this regimen is given we can only speculate as to any potential increased risk over and above what we have seen with the individual agent and combination regimens described above. Patients will be seen at least weekly so any toxicities can be detected and monitored carefully and treated as indicated. We will be particularly vigilant for pneumonitis which has been described for gemcitabine, albumin-bound paclitaxel and nivolumab (see below). We will be vigilant for nephritis and renal dysfunction, colitis and thyroid issues (hypo and hyper thyroidism), along with other immune related toxicities.

1.11 Study and Dose Rationale

Since we already have good safety data (and excellent prelimimary efficacy) of the albumin-bound paclitaxel + gemcitabine + cisplatin regimen with nivolumab we feel it is safe in this

phase II pilot trial to continue at the recommended dose of nivolumab which is 240mg dose and utilize that dose(see below). The dose of Nivolumab will be 240mg as a 60 minute infusion days 1, 15, 29, etc.

1.12 Sequence of Drug Administration and Rationale

The sequence of drug administration is nivolumab, albumin-bound paclitaxel, then cisplatin, then gemcitabine. Albumin-bound paclitaxel is given before the other chemotherapies because it may be taken up by the process of macropinocytosis. Then after adequate hydration (see Section 4.1), the cisplatin is given. Gemcitabine is given next because albumin-bound paclitaxel potentially decreases cytidine deaminase which potentiates gemcitabine activity (less degradation of gemcitabine by the enzyme).(Frese et al, 2012). Then paricalcitol is given last as it is in the ongoing SU2C neoadjuvant study.

2 OBJECTIVES

2.1 Primary Objective

The primary objective of this study is to determine the preliminary efficacy of the combination of nivolumab with albumin-bound paclitaxel plus paricalcitol plus cisplatin plus gemcitabine (the NAPPCG regimen) for patients with previously untreated (for their metastatic disease) metastatic pancreatic ductal cancer. This will be done by determining the complete response rate (CR), the overall response rate (ORR), progression free survival (PFS) and overall survival (OS).

2.2 Secondary Objective

The secondary objective of this study is to evaluate the safety of Nivolumab plus albumin-bound paclitaxel plus paricalcitol plus cisplatin plus gemcitabine in patients with previously untreated (for their metastatic disease) metastatic pancreatic ductal cancer. An additional objective is to evaluate self-reported quality of life and pain levels in this patient population.

2.3 Overview

This is a phase II pilot study evaluating the preliminary efficacy and safety of Nivolumab plus Albumin-bound Paclitaxel plus Paricalcitol plus Cisplatin plus Gemcitabine (NAPPCG) in patients with metastatic pancreatic ductal adenocarcinoma. Also, assessment of quality of life and pain levels will be explored in patients participating in this trial.

An individual cycle of therapy will be defined as six weeks (42 days). Multiple cycles may be administered until the patient is withdrawn from therapy.

Overall response rates as well as individual categories of response (CR, PR, SD, and PD) will be determined using RECIST 1.1 (Eisenhower 2009). Time-to-event endpoints, including PFS and OS will be assessed using the Kaplan-Meier method (Kaplan 1958). Evaluation of stable disease at 12 weeks will also be assessed. Toxicity (adverse events) will be recorded using the NCI CTCAE, version 4.0 (published 28 May 2009) (see Appendix D).

2.4 Primary Endpoints

- To evaluate the partial rate (PR) as defined by CT scan using RECIST 1.1 criteria. We expect to accomplish this in ≥ 40% of patients.
- If 4 or more of 10 patients demonstrate a partial response, we will continue to enroll to a total of 35 patients. Please note that to increase the number of patients enrolled from 10 to 35, more sites may need to be added to the study in order to reach enrollment goals.
- If intolerable adverse events or no clinical benefit are noted in the first 6 patients, we will discontinue study enrollment.

2.5 Secondary Endpoints

- To evaluate the disease control rate (CR, PR and SD at 12 weeks) in patients with metastatic PDA.
- To evaluate the treatment-related toxicities in this patient population.
- To evaluate the change in CA 19-9 (or CA 125, or CEA if not expressers of CA 19-9) in this patient population.

2.6 Exploratory Endpoints

- To evaluate the effects of combination therapy on immune biomarkers
- To evaluate cell-free DNA as biomarker for pancreatic cancer in relation to CA 19-9 and/or clinical response by RECIST 1.1
- To evaluate the commensal bacterial population and metabolites before and during anti-cancer immunotherapy along with correlating the patient's pre-treatment gut microbiome and mycobiome and the associated response to immunotherapy.
- To evaluate the individuals baseline tissue molecular profile as it relates to treatment outcome.

3 STUDY POPULATION

3.1 Patient Selection and Study Duration

This study will enroll up to 35 patients. The expected duration of this study is 36 months. Enrollment into the screening or treatment phase of the study will be stopped when the anticipated or actual patient numbers have been achieved across all study sites.

3.2 Inclusion Criteria

Patients must meet the following criteria to be included in the study:

1. Age ≥18 years of age.

2. Histologically or cytologically confirmed metastatic pancreatic ductal adenocarcinoma.

3. Capable of providing informed consent and complying with Trial procedures.

4. Karnofsky Performance Status (KPS) of ≥ 70%.

5. Life expectancy ≥ 12 weeks.

6. Measurable tumor lesions according to RECIST 1.1 criteria.

7. Women must not be able to become pregnant (e.g. post-menopausal for at least 1 year, surgically sterile, or agree to practice adequate birth control methods) for the duration of the study and for at least 5 months after the last dose of Nivolumab. Women of child bearing potential must have a negative serum or urine pregnancy test at the Screening Visit and be non-lactating. Both male and female patients of reproductive potential must agree to use a reliable method of birth control during the study and for at least 5 months (for women) and 7 months (for men with WOCBP partners) after last dose of Nivolumab.

3.3 Exclusion Criteria

Patients meeting the following criteria will not be enrolled:

1. Patients must have received no previous radiotherapy, surgery, chemotherapy or investigational therapy for the treatment of metastatic disease. Prior treatments in the adjuvant setting with gemcitabine and/or 5-FU or gemcitabine administered as a radiation sensitizer are allowed, provided at least 6 months have elapsed since completion of the last dose and no lingering toxicities are present.

2. Palliative surgery and/or radiation treatment less than 4 weeks prior to initiation of study treatment.

3. Exposure to any investigational agent within 4 weeks prior to initiation of study treatment.

4. Evidence of central nervous system (CNS) metastasis (negative imaging study, if clinically indicated, within 4 weeks of Screening Visit).

5. Malignancies other than pancreatic cancer ≤5 years prior to cycle 1 day 1, with the exception of those with a negligible risk of metastasis or death and treated with expected curative outcomes (such as adequately treated carcinoma in situ of the cervix, basal or squamous cell skin cancer or ductal carcinoma in situ treated surgically with curative intent) or localised prostate cancer treated with curative intent and absence of PSA relapse or incidental prostate cancer (Gleason score ≤3 +4 and PSA <10ng/L undergoing active surveillance and treatment naïve).

6. Laboratory values: Screening serum creatinine > 1.5 mg/dl; total bilirubin > (ULN); alanine aminotransferase (ALT) and AST ≥ 2.5 ULN or ≥ 3.0×ULN if liver metastases

are present; absolute neutrophil count <1,500/mm^3, platelet concentration <100,000/mm^3, hematocrit level <27% for females or <30% for males, or coagulation tests (prothrombin time [PT], partial thromboplastin time [PTT], International Normalized Ratio [INR]) >1.5×ULN unless on therapeutic doses of warfarin.

7. Current, serious, clinically significant cardiac arrhythmias as determined by the investigator.

8. History of HIV infection or active or chronic hepatitis B or C.

9. Active, clinically significant serious infection requiring treatment with antibiotics, anti-virals or anti-fungals.

10. Major surgery within 4 weeks prior to initiation of study treatment.

11. Any condition that might interfere with the patient's participation in the study or in the evaluation of the study results.

12. Any condition that is unstable and could jeopardize the patient's participation in the study.

13. Patient has a transplanted organ.

14. Patients with a history of autoimmune disease.

15. Prior PD-1 or PD-L1 therapy.

16. Patients taking systemic corticosteroids (equivalent to > 20mg hydrocortisone per day), or any other immunosuppressive therapy. Corticosteroids for treatment or prevention of nausea and vomiting, or to modulate symptoms from an event of suspected immunologic etiology are permitted. Inhaled (nasal or pulmonary), ophthalmic, topical steroids and local steroid injections are permitted.

17. Patients cannot have > Grade 1 pre-existing peripheral neuropathy (per CTCAE).

18. Women who are currently pregnant or breast-feeding or who are planning to become pregnant while on the study. This includes patients who are unwilling to use adequate birth control as described in inclusion criteria # 7.

19. Use of non-FDA approved cannabinoids are prohibited. Total daily useage of up to 40 mg per day of marinol is acceptable.

3.4 Patient Enrollment

This is an open-label study. A patient ID number will be assigned by the site when the patient signs the Informed Consent Form. A copy of the signed informed consent will be required for study entry.

The exact date and time of each administration of medications will be recorded in the case report form (CRF). Nivolumab, paricalcitol, cisplatin, albumin-bound paclitaxel and gemcitabine will be administered according to the clinical study protocol only to patients who have given written informed consent. Patients withdrawn from the study will retain their patient ID number. New patients must always be allotted a new patient ID number.

3.5 Patient Discontinuation

Patients will be discontinued from the treatment under the following circumstances:

1. Disease progression.
2. Patient's physician considers a change of therapy would be in the best interest of the patient.
3. Patient requests discontinuation.
4. Continued unacceptable toxicities despite optimal treatment or dose reduction.
5. Patient becomes pregnant or fails to use adequate birth control (for those patients who are fertile).
6. Need for any treatment not allowed by the protocol.
7. Non-compliance.

3.6 Study Discontinuation

HonorHealth has the right to terminate the participation of either an individual site or the study at any time. Reasons for terminating the study include, but are not limited to, the following:

1. Incidence or severity of AEs in this or other studies indicates a potential health hazard to patients.
2. Patient enrollment is unsatisfactory.
3. Investigator does not adhere to the protocol or applicable regulatory guidelines in conducting the study.
4. If a study protocol and procedure are deemed unsafe by the data safety and monitoring committee.

4 STUDY TREATMENT

4.1 Administration and Dosing

Treatment must be administered in a hospital, clinic or other out-patient setting appropriate for chemotherapeutic infusions. No investigational or commercial agents or therapies other than those described may be administered with the intent to treat the patient's malignancy.
The names, titles, and addresses of the Investigators and study personnel who administer the study medication will be listed in the Site Contacts list for Protocol NAPPCG-EB 2015-001 and will be available from HonorHealth or its representative.

The solution for infusion will be prepared at each investigational site, as outlined below. Guidance for preparation, compatibilities, stability and administration of nivolumab, paricalcitol, albumin-bound paclitaxel, cisplatin and gemcitabine are provided in each drug's Prescribing Information document, referenced in Appendix E. There will be an administration window of -5/+30 minutes. The order of infusion with premedication is as follows:

- Nivolumab will be given every two weeks as a 60 minute IV infusion. The dose will be 240 mg fixed dose every two weeks.

- Pre cisplatin hydration: 0.9% Sodium Chloride Injection 1000 mL with Mannitol 12.5 grams and Magnesium Sulfate 2 grams IV infusion over 2 hours on days 1, 8, 22 and 29 repeated every 42 days. NOTE: if supply of Mannitol is limited, then dose according to institutional policy and procedure. Pre cisplatin hydration may be given prior to the nivolumab.

- Palonosetron (Aloxi®) 0.25 mg IV, fosaprepitant (Emend®) 150 mg IV and dexamethasone 12 mg IV within 30 minutes prior to treatment on days patient is receiving albumin-bound paclitaxel + cisplatin + gemcitabine. (See Appendix H for details of reduced dosing of dexamethasone with concomitant administration of fosaprepitant). Patients will continue oral antiemetic prophylaxis at home with ondansetron 8 mg bid and dexamethasone 4 mg twice daily for 2 days after chemotherapy. Olanzapine 10 mg PO at bedtime x 3 days can be considered if additional antiemetic is needed. The type of antiemetic prophylaxis used can vary based on institutional procedures.
- Albumin-bound paclitaxel 125 mg/m^2 over 30 minute IV infusion on days 1, 8, 22, and 29 repeated every 42 days, followed by:
- Cisplatin 25 mg/m2 in 500* mL of NS over 60 minute IV infusion on days 1, 8, 22, and 29 repeated every 42 days, followed by:
- Gemcitabine 1000 mg/m2 in 500* mL over 30 minute IV infusion on days 1, 8, 22, and 29 repeated every 42 days
- Post cisplatin hydration: 0.9% Sodium Chloride Injection 1000* mL IV infusion over 3 hours on days cisplatin is administered. May start at the same time as the gemcitabine infusion.
- Paricalcitol will be given at a dose of 25 micrograms days 1, 4, 8, 12, 15, 18, 22, 26, 29, 32, 36, and 39 repeated every 42 days +/- 1 day allowed for dosing

The investigator may reduce the volume of 0.9% Sodium Chloride Injection to 250 mL for cisplatin and gemcitabine and/or post hydration volume to 500 mL if clinically indicated. The use of additive electrolytes (i.e. Magnesium, Potassium) may also be added if clinically indicated.

In the event of extravasation during the infusion of Nivolumab, albumin-bound paclitaxel, paricalcitol, cisplatin or gemcitabine, the infusion should be immediately terminated and patients treated according to local site protocols. The infusion should then be restarted in another vein.

4.2 Body Surface Area Calculation

The calculation of the dose of cisplatin, gemcitabine, and albumin-bound paclitaxel will be based on the patient's body surface area (BSA) using the Mosteller formula (Verbraeken 2006). The BSA will be calculated before each new cycle, based on the actual height and weight of the patient. If there has been a > 10% weight change from baseline, the drug doses will be recalculated based on the new BSA value. Doses are rounded to the nearest whole milligram. The dose of paricalcitol will be a flat dose of 25 micrograms. The dose of nivolumab will be a flat dose of 240 mg.

4.3 Dose Modification for Toxicity

Toxicities will be graded using the NCI CTCAE v4.0 (see Appendix D). If toxicity occurs during or after any treatment cycle, the toxicity will be graded and appropriate supportive care treatment may be administered to decrease the signs and symptoms (e.g. antiemetics, antidiarrheals, antipyretics, antihistamines).

4.3.1 For Nivolumab

For management of immune-oncology adverse events related to Nivolumab therapy, please refer to section 4.5.4 and Appendix G. Warnings and precautions regarding treatment with Nivolumab can be found in the Nivolumab Prescribing Information, link in Appendix E.

4.3.2 For albumin-bound paclitaxel or gemcitabine or cisplatin or paricalcitol

Doses of albumin-bound paclitaxel and gemcitabine may be reduced in individual patients in accordance with the schedule in Tables 2, 3, 4, 5 and 6. In general, doses that have been reduced for toxicity will not be escalated back to the starting level. Growth factors may be used to treat hematologic toxicity and will not constitute a dose reduction.

Table 2 Dose Reduction Schema

Dose Level	albumin-bound Paclitaxel (mg/m2)	Cisplatin Dose** (mg/m2)	Gemcitabine (mg/m2)	Paricalcitol* (micrograms)
Level - 0 (baseline)	125mg/m^2	25**	1000mg/m^2	25 micrograms
Level -1	100mg/m^2	25**	800mg/m^2	25 micrograms
Level -2	75mg/m^2	25**	600mg/m^2	25 micrograms

*Note if any toxicity is deemed certainly relatable to the paricalcitol (e.g. renal stone, etc.) the paricalcitol will be discontinued

**Note cisplatin should not be given unless creatinine is < 1.5 mg/dl.

4.3.2.1 Hematological Toxicity

In the event dose modifications are required at the beginning of a cycle or within a cycle due to hematologic toxicities, doses of albumin-bound paclitaxel, cisplatin, and gemcitabine may be adjusted as detailed in Table 2. Please note that all 5 drugs will be held at the start of a new cycle if Table 3 criteria are not met.

Dose Modifications at Day 1 or Day 22

Table 3 Dose Modifications for Day 1 or Day 22 of Each Cycle with a cycle being defined as 42 days (Hematologic Toxicity)

ANC		Platelets	Timing
≥ 1.5 x 10^9/L	And	≥ 100 x 10^9/L	Treat on time
< 1.5 x 10^9/L	Or	< 100 x 10^9/L	No treatment

Dose Adjustments within a Treatment Cycle

In the event that patients have missed doses within a treatment cycle due to hematologic toxicities, those doses not given during a cycle will not be made up. Dose modifications due to hematologic toxicity (as represented by the blood counts and toxicities, below) within a treatment cycle should be adjusted as outlined in Table 3.

Table 4 Dose Modification for Days 8 or 29 of Each Cycle (Hematologic Toxicity)*

Day 8 or 29 Laboratory Results	Day 8 or 29 Album-bound paclitaxel	Day 8 or 29 Cisplatin	Day 8 or 29 Gemcitabine	Day 29 Nivolumab	Days 8 or 29 Paricalcitol
ANC > 1000 and Platelets ≥ 75,000	100%	100%	100%	100%	100%
ANC 500-1000[a] or Platelets 50,000-74,999	Decrease dose by 1 level (treat on time)	100%	Decrease dose by 1 level (treat on time)	100%	100%
ANC < 500 or Platelets < 50,000	Hold	Hold	Hold	Hold	100%
Febrile Neutropenia (Grade 3 or 4)[b]	Hold. Upon resuming dosing, decrease to next lower dose level and do not re-escalate throughout the rest of treatment	Hold	Hold. Upon resuming dosing, decrease to next lower dose level and do not re-escalate throughout the rest of treatment	Hold	100%
Recurrent Febrile Neutropenia (Grade 3 or 4) [b]	Hold. Upon resuming dosing, decrease 2 dose levels (to 75 mg/m2) and do not re-escalate throughout the rest of treatment	Hold	Hold. Upon resuming dosing, decrease 2 dose levels (to 600 mg/m2) and do not re-escalate throughout the rest of treatment.	Hold	100%

* see Table 2 for dose reduction schedule

[a] If patients do not experience resolution of neutropenia within 21 days, despite uninterrupted G-CSF treatment, study treatment will be discontinued.

[b] Febrile patients (regardless of neutrophil count) should have their chemotherapy treatment interrupted. A full sepsis diagnostic work-up should be performed while continuing broad spectrum antibiotics. If cultures are positive, the antibiotic may or may not be changed, depending on the sensitivity profile of the isolated organism. Patients with persisting fever after 3 weeks, despite uninterrupted antibiotic treatment, will discontinue study treatment. Febrile neutropenic patients can also receive G-CSF, in addition to antibiotic treatment, to hasten the resolution of their febrile neutropenia (following current institutional guidelines). In all cases, blood counts must have returned to baseline levels before resuming chemotherapy treatment.

4.3.2.2 Non-hematological Toxicity

Dose reductions for non-hematologic toxicity that occur despite adequate background medical therapy should be undertaken in accordance with Table 5.

Table 5 Albumin-bound paclitaxel and gemcitabine and cisplatin - Dose Modifications for Day 1 or Day 22 of Each Cycle (Non-hematologic Toxicity)*

Non Hematologic Toxicity and/or Dose Hold with Previous Cycle	
Toxicity/dose held	**Albumin-bound paclitaxel + gemcitabine + cisplatin dose this cycle**
Grade 0, 1 or 2 toxicity	Same as Day 1 previous cycle (except for Grade 2 cutaneous toxicity where doses of albumin-bound paclitaxel and gemcitabine should be reduced to next lower dose level: please refer to Section 4.3.2.5**).** Note cisplatin should not be given unless creatinine is < 1.5 mg/dL.
Grade 3 toxicity[a,c]	Decrease albumin-bound paclitaxel and gemcitabine to next lower dose level[a] (see table 1)
Grade 4 toxicity[b]	Off protocol treatment[b]
Dose held in 2 previous consecutive cycles	Decrease albumin-bound paclitaxel and gemcitabine to next lower dose level and continue throughout the rest of treatment

* Excluding peripheral neuropathy (section 4.3.2.3) and nephrotoxicity (section 4.3.2.4).

[a] If the toxicity only affects neuropathy, then only albumin-bound paclitaxel should be reduced (please see Section 4.3.2.3).

[b] Pulmonary embolism (a Grade 4 toxicity in the CTCAE tables) if mild or asymptomatic, will be exempt from this requirement (please see Section 4.3.2.7).

[c] Excluding electrolyte abnormalities per judgment of the physician/investigator.

Table 6 Albumin-bound paclitaxel and gemcitabine and cisplatin Dose Modifications Day 8 or 29 of Each Cycle (Non-hematological Toxicity)

CTC Grade	**Percent of Day 1 *albumin-bound* paclitaxel + gemcitabine + cisplatin Dose**
0-2	100%[a]
3+	Hold treatment until resolution to ≤ Grade 1 [b,c].

[a] Except for cutaneous toxicity: please refer to Section 4.3.2.5.

[b] Pulmonary embolism (a Grade 4 toxicity in the CTCAE tables) if mild or asymptomatic, will be exempt from this requirement (please see Section 4.3.2.7).

[c] Excluding electrolyte abnormalities per judgment of the physician/investigator.

Please note when one drug is discontinued then it will be a matter of patient situation and clinical judgement as to whether some or all of the other agents are discontinued.

4.3.2.3 Peripheral Neuropathy

Cisplatin and albumin-bound paclitaxel treatment should be withheld in patients who experience ≥ Grade 3 peripheral neuropathy. Gemcitabine, nivolumab and paricalcitol administration can continue during this period. Cisplatin may be resumed at the same dose and albumin-bound paclitaxel treatment may be resumed at the next lower dose level in subsequent cycles after the peripheral neuropathy improves to ≤ Grade 1. The time to resolution to Grade ≤ 1 should be the adverse event duration used for adverse event reporting.

4.3.2.4 Nephrotoxicity

Cisplatin (cisplatin injection) produces cumulative nephrotoxicity which is potentiated by aminoglycoside antibiotics (see Appendix E). The serum creatinine, BUN, creatinine clearance, and magnesium, sodium, potassium, and calcium levels should be measured prior to initiating therapy, and prior to each subsequent course. Cisplatin should not be given unless serum creatinine is < 1.5 mg/dL .

Please also note that as detailed in sections 1.3. that nivolumab can also cause immune mediated nephritis and renal dysfunction. Please see section 4.5 and Appendix G for delay/discontinuation instructions.

4.3.2.5 Cutaneous Toxicity

Patients who develop Grade 2 or 3 cutaneous toxicity due to gemcitabine or albumin-bound paclitaxel should have their doses reduced to the next lower dose level as per Table 2. If the patient continues to experience these reactions, despite dose reduction, treatment should be discontinued. Patients who develop Grade 4 cutaneous toxicity should have treatment discontinued.

4.3.2.6 Gastrointestinal Toxicity

If Grade 3 mucositis or diarrhea occurs, all 5 study drugs should be withheld until resolution to ≤ Grade 1, then dose reduced as per Table 2.

Please also note that as detailed in section 1.3 that nivolumab also causes colitis/diarrhea. Please see section 4.5 and Appendix G for delay/discontinuation instructions for Nivolumab. Patients who develop Grade 3 or 4 mucositis or diarrhea that is related to Nivolumab should have treatment discontinued as per management algorithms.

4.3.2.7 Pulmonary Embolism

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

4.3.2.8 Interstitial Pneumonitis

Pulmonary toxicity has been reported for gemcitabine, paclitaxel, and for nivolumab. Epidemiology reports show that gemcitabine monotherapy is weakly associated with lung toxicity. A retrospective review (Meadors et al, 2006) of pooled clinical trial data of 4,448 patients with mixed cancer indications reported an incidence of dyspnea of 0.2% and serious pulmonary toxicity of 0.06%. Paclitaxel monotherapy is weakly associated with lung toxicity (Rowinsky and Donnehouer 1995). Dyspnea with bronchospasm has been reported in 0.3 to 0.9%, with 30% of type 1 hypersensitivity reactions. Combination chemotherapy of gemcitabine and albumin-bound paclitaxel shows a higher incidence of this complication compared to either drug alone but the two are no more than additive (Von Hoff et al, 2013). Please see section 4.5 for details on nivolumab pneumonitis.

During study participation, patients should be carefully monitored for signs and symptoms of pneumonitis (i.e. episodes of transient or repeated dyspnea with unproductive persistent cough or fever) and, if observed, immediate clinical evaluation and timely institution of appropriate management (emphasizing the need for corticosteroids if an infectious process has been ruled

out as well as appropriate ventilation and oxygen support when required). Administration of study drugs will be permanently discontinued upon making a diagnosis of interstitial pneumonitis. (See Section below and also see 4.5 for additional management, particularly for the possible nivolumab complications)

Prevention, Surveillance and Management of Interstitial Pneumonitis

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

- Infections should be ruled out with routine immunological/ microbiological methods. Transbronchial lung biopsy is not recommended, given its limited value and risk of pneumothorax and hemorrhage, and should be reserved for cases with unclear etiology.

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

4.3.2.9 Hypersensitivity Reactions

Hypersensitivity reactions are not usually expected with cisplatin, albumin-bound 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 offending agent and aggressive symptomatic therapy. Patients who develop a severe hypersensitivity reaction should not be re-challenged. Please see section 4.5 for details on possible nivolumab immune reaction.

4.3.2.10 Colony Stimulating Factors

Based on the ASCO guidelines (Smith 2006) for use of granulocyte colony stimulating factors, (G-CSF) for regimens with at least a 20% risk of febrile neutropenia, pegfilgrastim will be administered subcutaneously on day 9 & 30 of each treatment cycle. G-CSF may also be given according to institutional guidelines for the treatment of neutropenic fever or infections associated with neutropenia and for the prevention of febrile neutropenia in patients with an ANC < 500 cells/μL (see Appendix F). Patients not experiencing resolution of neutropenia within 21 days, despite uninterrupted G-CSF treatment, will discontinue study treatment.

4.3.2.11 Prophylaxis against Sepsis

Due to the incidences of non-neutropenic sepsis, at the first occurrence of fever ≥ 38.5°C (regardless of neutrophil count), institution of ciprofloxacin (500 mg orally, twice daily) or amoxicillin/clavulanate (Augmentin®, 500 mg orally, 2-3 times daily) in patients with allergy to fluoroquinolones should be initiated. On their first visit, patients should be provided with enough ciprofloxacin (or the alternative antibiotic) for use at home, and they should be instructed to begin taking it when they first record a temperature of ≥ 38.5 °C (or if they feel they are developing a fever and a thermometer is not available). They should also immediately contact their physician for guidance on where to go for blood counts and to be evaluated for sepsis as soon as possible. Hospitalization or evaluation in the emergency room may be required depending on the clinical presentation. If hospitalization is required, please refer to Section 7.7 of this protocol to report the event as a Serious Adverse Event (SAE).

4.3.3 Intended Dose Delays

Intended cycles may be delayed for non-toxicity reasons for up to 14 days (for reasons such as scheduling conflicts), but only with documentation and explanation in the CRF after discussion with the study Principal Investigator.

4.4 Special Warning and Precautions and Management for Possible Nivolumab Complications (See Nivolumab Prescribing Information for detailed AE incidence in key approval trials).

4.4.1 Immune –Mediated Pneumonitis

Nivolumab can cause immune-mediated pneumonitis, defined as requiring use of corticosteroids and no clear alternate etiology. Fatal cases have been reported. In patients receiving nivolumab as a single agent, immune-mediated pneumonitis occurred in 3.1% (61/1994) of patients. The median time to onset of immune-mediated pneumonitis was 3.5 months (range: 1 day to 22.3 months). Immune-mediated pneumonitis led to permanent discontinuation of nivolumab in 1.1%, and withholding of nivolumab in 1.3% of patients. Approximately 89% of patients with pneumonitis received high-dose corticosteroids (at least 40 mg prednisone equivalents per day) for a median duration of 26 days (range: 1 day to 6 months). Complete resolution of symptoms following corticosteroid taper occurred in 67% of patients. Approximately 8% of patients had recurrence of pneumonitis after re-initiation of nivolumab.

Monitor patients for signs and symptoms of pneumonitis. Administer corticosteroids at a dose of 1 to 2 mg/kg/day prednisone equivalents for moderate (Grade 2), or up to 4 mg/kg/day prednisone equivalents for more severe (Grade 3-4) pneumonitis, followed by corticosteroid taper. Permanently discontinue nivolumab for severe (Grade 3) or life-threatening (Grade 4) pneumonitis and withhold nivolumab until resolution for moderate (Grade2) pneumonitis.

See Appendix G for Management Algorithms for Adverse Events Related to Nivolumab Therapy.

4.4.2 Immune-Mediated Colitis

Nivolumab can cause immune-mediated colitis, defined as requiring use of corticosteroids with no clear alternate etiology. In patients receiving nivolumab as a single agent, immune-mediated colitis occurred in 2.9% (58/1994) of patients; the median time to onset was 5.3 months (range:

2 days to 20.9 months). Immune-mediated colitis led to permanent discontinuation of nivolumab in 0.7% and withholding of nivolumab in 1% of patients. Approximately 91% of patients with colitis received high-dose corticosteroids (at least 40 mg prednisone equivalents per day) for a median duration of 23 days (range: 1 day to 9.3 months). Four patients required addition of infliximab to high-dose corticosteroids. Complete resolution occurred in 74% of patients. Approximately 16% of patients had recurrence of colitis after re-initiation of nivolumab.

Monitor patients for immune-mediated colitis. Administer corticosteroids at a dose of 1 to 2 mg/kg/day prednisone equivalents followed by corticosteroid taper for severe (Grade 3) or life threatening (Grade 4) colitis. Administer corticosteroids at a dose of 0.5 to 1 mg/kg/day prednisone equivalents followed by corticosteroid taper for moderate (Grade 2) of more than 5 days duration: if worsening or no improvement occurs despite initiation of corticosteroids, increase dose to 1 to 2 mg/kg/day prednisone equivalents. Withhold nivolumab for Grade 2 or 3 immune-mediated colitis. Permanently discontinue nivolumab for Grade 4 colitis or for recurrent colitis upon restarting nivolumab.

See Appendix G for Management Algorithms for Adverse Events Related to Nivolumab Therapy.

4.4.3 Immune-mediated Hepatitis

Nivolumab can cause immune-mediated hepatitis, defined as requiring use of corticosteroids and no clear alternate etiology. In patients receiving nivolumab as a single agent, immune-mediated hepatitis occurred in 1.8% (35/1994) of patients; the median time to onset was 3.3 months (range: 6 days to 9 months). Immune-mediated hepatitis led to permanent discontinuation of nivolumab in 0.7% and withholding of nivolumab in 1% of patients. All patients with hepatitis received high-dose corticosteroids (at least 40 mg prednisone equivalents) for a median duration of 23 days (range: 1 day to 2 months). Two patients required the addition of mycophenolic acid to high-dose corticosteroids. Complete resolution occurred in 74% of patients. Approximately 29% of patients had recurrence of hepatitis after re-initiation of nivolumab.

Monitor patients for abnormal liver tests prior to and periodically during treatment. Administer corticosteroids at a dose of 1 to 2 mg/kg/day prednisone equivalents followed by corticosteroid taper for severe (Grade 3) or life-threatening (Grade 4) transaminase elevations, with or without concomitant elevation in total bilirubin. Administer corticosteroids at a dose of 0.5 to 1 mg/kg/day prednisone equivalents followed by corticosteroid taper for moderate (Grade 2) transaminase elevations. Withhold nivolumab for moderate (Grade 2) and permanently discontinue nivolumab for severe (Grade 3) or life-threatening (Grade 4) immune-mediated hepatitis.

See Appendix G for Management Algorithms for Adverse Events Related to Nivolumab Therapy.

4.4.4 Immune-Mediated Nephritis and Renal Dysfunction

Nivolumab can cause immune-mediated nephritis, defined as renal dysfunction or ≥Grade 2 increased creatinine, requirement for corticosteroids, and no clear alternate etiology. In patients receiving nivolumab as a single agent, immune-mediated nephritis and renal dysfunction occurred in 1.2% (23/1994) of patients; the median time to onset was 4.6 months (range: 23 days to 12.3 months). Immune-mediated nephritis and renal dysfunction led to permanent discontinuation of nivolumab in 0.3% and withholding of nivolumab in 0.8% of patients. All patients received high-dose corticosteroids (at least 40 mg prednisone equivalents per day) for

a median duration of 21 days (range: 1 day to 15.4 months). Complete resolution occurred in 48% of patients. No patients had recurrence of nephritis or renal dysfunction after re-initiation of nivolumab.

Monitor patients for elevated serum creatinine prior to and periodically during treatment. Administer corticosteroids at a dose of 1 to 2 mg/kg/day prednisone equivalents followed by corticosteroid taper for life-threatening (Grade 4) serum creatinine elevation and permanently discontinue nivolumab. For severe (Grade 3) or moderate (Grade 2) serum creatinine elevation, withhold nivolumab and administer corticosteroids at a dose of 0.5 to 1 mg/kg/day prednisone equivalents followed by corticosteroid taper, if worsening or no improvement occurs, increase dose of corticosteroids to 1 to 2 mg/kg/day prednisone equivalents and permanently discontinue Nivolumab.

See Appendix G for Management Algorithms for Adverse Events Related to Nivolumab Therapy.

4.4.5 Immune-Mediated Endocrinopathies

4.4.5.1 Hypophysitis

In patients receiving nivolumab as a single agent, hypophysitis occurred in 0.6% (12/1994) of patients; the median time to onset was 4.9 months (range: 1.4 to 11 months). Hypophysitis led to permanent discontinuation of nivolumab in 0.1% and withholding of nivolumab in 0.2% of patients. Approximately 67% of patients with hypophysitis received hormone replacement therapy and 33% received high-dose corticosteroids (at least 40 mg prednisone equivalents per day) for a median duration of 14 days (range: 5 to 26 days).
Monitor patients for signs and symptoms of hypophysitis. Administer hormone replacement as clinically indicated and corticosteroids at a dose of 1 mg/kg/day prednisone equivalents followed by corticosteroid taper for moderate (Grade 2) or greater hypophysitis. Withhold nivolumab for moderate (Grade 2) or severe (Grade 3). Permanently discontinue nivolumab for life-threatening (Grade 4) hypophysitis.

4.4.5.2 Adrenal Insufficiency

In patients receiving nivolumab as a single agent, adrenal insufficiency occurred in 1% (20/1994) of patients and the median time to onset was 4.3 months (range: 15 days to 21 months). Adrenal insufficiency led to permanent discontinuation of nivolumab in 0.1% and withholding of nivolumab in 0.5% of patients. Approximately 85% of patients with adrenal insufficiency received hormone replacement therapy and 25% received high-dose corticosteroids (at least 40 mg prednisone equivalents per day) for a median duration of 11 days (range: 1 day to 1 month).
Monitor patients for signs and symptoms of adrenal insufficiency. Administer corticosteroids at a dose of 1 to 2 mg/kg/day prednisone equivalents followed by a corticosteroid taper for severe (Grade 3) or life-threatening (Grade 4) adrenal insufficiency. Withhold nivolumab for moderate (Grade 2) and permanently discontinue nivolumab for severe (Grade 3) or life-threatening (Grade 4) adrenal insufficiency.

4.4.5.3 Hypothyroidism and Hyperthyroidism

In patients receiving nivolumab as a single agent, hypothyroidism or thyroiditis resulting in hypothyroidism occurred in 9% (171/1994) of patients; the median time to onset was 2.9 months (range: 1 day to 16.6 months). Approximately 79% of patients with hypothyroidism received levothyroxine and 4% also required corticosteroids. Resolution occurred in 35% of patients.

Hyperthyroidism occurred in 2.7% (54/1994) of patients receiving nivolumab as a single agent; the median time to onset was 1.5 months (range: 1 day to 14.2 months). Approximately 26% of patients with hyperthyroidism received methimazole, 9% received carbimazole, 4% received propylthiouracil, and 9% received corticosteroids. Resolution occurred in 76% of patients.

Monitor thyroid function prior to and periodically during treatment. Administer hormone replacement therapy for hypothyroidism. Initiate medical management for control of hyperthyroidism. There are no recommended dose adjustments of nivolumab for hypothyroidism or hyperthyroidism.

4.4.5.4 Type 1 Diabetes Mellitus

In patients receiving nivolumab as a single agent, diabetes occurred in 0.9% (17/1994) of patients including two cases of diabetic ketoacidosis. The median time to onset was 4.4 months (range: 15 days to 22 months).
Monitor for hyperglycemia. Withhold nivolumab in cases of severe (Grade 3) hyperglycemia until metabolic control is achieved. Permanently discontinue nivolumab for life-threatening (Grade 4) hyperglycemia.
See Appendix G for Management Algorithms for Adverse Events Related to Nivolumab Therapy.

4.4.6 Immune-Mediated Skin Adverse Reactions

Nivolumab can cause immune-mediated rash, including Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN), some cases with fatal outcome. In patients receiving nivolumab as a single agent, immune-mediated rash occurred in 9% (171/1994) of patients; the median time to onset was 2.8 months (range: <1 day to 25.8 months). Immune-mediated rash led to permanent discontinuation of nivolumab in 0.3% and withholding of nivolumab in 0.8% of patients. Approximately 16% of patients with rash received high-dose corticosteroids (at least 40 mg prednisone equivalents per day) for a median duration of 12 days (range: 1 days to 8.9 months) and 85% received topical corticosteroids. Complete resolution occurred in 48% of patients. Recurrence of rash occurred in 1.4% of patients who resumed nivolumab after resolution of rash.

For symptoms or signs of SJS or TEN, withhold nivolumab and refer the patient for specialized care for assessment and treatment. If SJS or TEN is confirmed, permanently discontinue nivolumab.

For immune-mediated rash, administer corticosteroids at a dose of 1 to 2 mg/kg/day prednisone equivalents followed by a corticosteroid taper for severe (Grade 3) or life-threatening (Grade 4) rash. Withhold nivolumab for severe (Grade 3) rash and permanently discontinue nivolumab for life-threatening (Grade 4) rash.

See Appendix G for Management Algorithms for Adverse Events Related to Nivolumab Therapy.

4.4.7 Immune-Mediated Encephalitis

Nivolumab can cause immune-mediated encephalitis with no clear alternate etiology. Evaluation of patients with neurologic symptoms may include, but not be limited to, consultation with a neurologist, brain MRI, and lumbar puncture.
In patients receiving nivolumab as a single agent, encephalitis occurred in 0.2% (3/1994). Fatal limbic encephalitis occurred in one patient after 7.2 months of exposure despite discontinuation

of nivolumab and administration of corticosteroids. In the other two patients encephalitis occurred post-allogeneic HSCT.
Withhold nivolumab in patients with new-onset moderate to severe neurologic signs or symptoms and evaluate to rule out infectious or other causes of moderate to severe neurologic deterioration. If other etiologies are ruled out, administer corticosteroids at a dose of 1 to 2 mg/kg/day prednisone equivalents for patients with immune-mediated encephalitis, followed by corticosteroid taper. Permanently discontinue nivolumab for immune-mediated encephalitis.

See Appendix G for Management Algorithms for Adverse Events Related to Nivolumab Therapy.

4.4.8 Other Immune-Mediated Adverse Reactions

Nivolumab can cause other clinically significant immune-mediated adverse reactions. Across clinical trials of nivolumab administered as a single agent or in combination with ipilimumab, the following clinically significant immune-mediated adverse reactions occurred in less than 1.0% of patients receiving nivolumab: uveitis, iritis, pancreatitis, facial and abducens nerve paresis, demyelination, polymyalgia rheumatica, autoimmune neuropathy, Guillain-Barre syndrome, hypopituitarism, systemic inflammatory response syndrome, gastritis, duodenitis, sarcoidosis, histiocytic necrotizing lymphadenitis (Kikuchi lymphadenitis), myositis, myocarditis, rhabdomyolysis, motor dysfunction, vasculitis, and myasthenic syndrome.

For any suspected immune-mediated adverse reactions, exclude other causes. Based on the severity of the adverse reaction, permanently discontinue or withhold nivolumab, administer high-dose corticosteroids, and if appropriate, initiate hormone-replacement therapy. Upon improvement to Grade 1 or less, initiate corticosteroid taper and continue to taper over at least 1 month. Consider restarting nivolumab after completion of corticosteroid taper based on the severity of the event.

4.4.9 Infusion Reactions

Nivolumab can cause *severe* infusion reactions, which have been reported in less than 1.0% of patients in clinical trials. In patients receiving nivolumab as a single agent, infusion-related reactions occurred in 6.4% (127/1994) of patients.

Discontinue nivolumab in patients with severe or life-threatening infusion reactions. Interrupt or slow the rate of infusion in patients with mild or moderate infusion reactions.

4.5 Concomitant Therapy

Necessary supportive measures for optimal medical care may be given throughout the study, including IV antibiotics to treat infections, blood components, and antiemetics. Additional care will be administered as indicated by the treating physician and the patient's medical need. All concomitant medications and supportive therapy must be recorded on the appropriate CRF.

4.5.1 Prohibited Concomitant Therapy

No concomitant cytotoxic therapy, whether conventional or investigational, will be allowed during this study.

Immunosuppressive corticosteroid use is not permitted while enrolled in the study. Corticosteroids for treatment or prevention of nausea and vomiting, or to modulate symptoms from an event of suspected immunologic etiology are permitted. Inhaled (nasal or pulmonary), ophthalmic, topical steroids and local steroid injections are permitted.

Radiotherapy is not allowed while the patient is enrolled in this study.

The use of vitamins or supplements that have reported use for the treatment or prevention of cancer, or that may interact with any of the study medications is not permitted.

The use of medical marijuana (except FDA-approved therapy) in any formulation should be avoided while enrolled in this study.

The use of additional vitamin D supplements beyond replacement while receiving study-administered paricalcitol should be avoided

4.5.2 Permitted Concomitant Therapy

Routine **prophylactic use** of a granulocyte colony-stimulating factor (G-CSF) will be used according to the American Society of Clinical Oncology guidelines (Appendix F), on Day 9 and 30 of the 42 days cycle.

The use of erythropoietin stimulating agents (ESA) is permitted if clinically indicated.

4.5.3 Concomitant Therapies Requiring Caution

Cisplatin nephrotoxicity may be exacerbated by treatment with other nephrotoxic drugs (e.g. aminoglycoside antibiotics, non-steroidal anti-inflammatory drugs). Caution with use of other nephrotoxic drugs.

If anticoagulation with warfarin is necessary, frequent monitoring of prothrombin time and the International Normalized Ratio (INR) is recommended. Please see Appendix H for special precautions on the use of dexamethasone with concomitant fosaprepitant.

5 STUDY ASSESSMENTS

5.1 Laboratory Assessments

All hematology, blood chemistries, urinalyses, and serum or urine pregnancy tests (if applicable) will be performed by the local laboratory at each investigational site.
Prior to study enrollment, each patient will have the following assessments (see Appendix A).

5.2 Quality of life and Pain Assessments

Two well-known tools will be utilized to assess participant's self-reported quality of life and pain levels during this study. The MD Anderson Symptom Inventory (MDASI-GI) and Brief Pain Inventory (BPI) are valid, reliable, and sensitive instruments for assessing the severity of symptoms and their interference in patients' daily functioning. The MDASI asks patients to rate the worst severity of symptoms during the past 24 hours (0 not present to 10 as bad as you can

imagine). It also rates the extent to which symptoms interfere with various aspects of life (e.g., general activity, mood, relations with other people, and enjoyment of life) using a scale ranging from 0 (did not interfere) to 10 (interfered completely). The BPI uses four pain severity items rated with a 0 to 10 numeric rating scale (NRS); the interference scale is similar to the MDASI (0 = no interference to 10 = interferes completely). Internal consistency measures (reliability) in prior studies were high at 0.80 or more (Cronbach alpha) for the BPI and MDASI (Atkinson et al, 2010; Cleeland et al, 2000; Janjan et al, 2007; Wang et al, 2010).

Instruments will be administered at screening, weekly throughout treatment and at end of study. Please see Appendix L and M for information on instruments.

5.3 Exploratory Biomarkers

At Screening, individuals with core biopsies obtained previously will be obtained by the investigator's site for further exploratory analysis. Up to a total of 7 micron slice slides will be obtained or a cellular block of tumor tissue. Future analysis will include PD-1, interferon gamma, B-catenin, and other immunological assays along with those that will assess for sensitivity to DNA repair targeted therapy. The sites may send the unstained core samples to HonorHealth to be stored at room temperature and will be analyzed at a later date.

At screening and Day 39 stool sample collection kits will be distriuted for microbiome and mycobiome analysis. The stool sample needs to be returned to the site within 72 hours of collection. Prior analysis has shown correlation with the microbiome and mycobiome and treatment response along with toxicity [Frankel et al 2017, Gopalakrishnan et al 2018, Chaput et al 2017].

On cycle 1 day 1 (up to 72 hours before) and every subsequent cycle until an individual stops participating in the study, 20 mLs of blood will be collected for exploratory analyses.

5.4 Screening (Within 21 Days Prior to First Dose)

- Written informed consent
- Review inclusion and exclusion criteria
- Complete medical and surgical history including concurrent baseline conditions (using NCI CTCAE version 4.0; Appendix D).
- Prior cancer therapy (including documentation of prior surgery, adjuvant or neoadjuvant chemotherapy and radiotherapy)
- Complete physical examination including height (cm) and weight (kg)
- Karnofsky Performance Status (KPS) (see Appendix B)
- Vital signs (blood pressure, pulse, respiratory rate, and temperature)
- Computed tomography (CT)/magnetic resonance imaging (MRI) scan to document disease status (including chest, abdomen, pelvis, and other regions as clinically indicated. In addition, brain scan is required to exclude brain metastases if clinically indicated only. If a CT scan was taken within 28 days prior to first dose, a new scan is not necessary. However, if a new scan is to be done, it should be performed as close to the start of chemotherapy as possible. (See RECIST 1.1 criteria in Section 6). In addition, a baseline PET is desirable.
- Electrocardiogram (ECG)
- Complete blood count (CBC) with differential and platelet count

- Serum chemistries (for hepatic and renal function tests) including blood urea nitrogen (BUN), phosphorus, magnesium, creatinine, creatinine clearance, total protein, albumin, calcium, glucose, total bilirubin, alkaline phosphatase (ALP), aspartate aminotransferase (AST), alanine aminotransferase (ALT), and electrolytes (chloride, sodium, potassium, and bicarbonate)
- Vitamin D serum level
- Coagulation panel including PTT and PT/INR
- Thyroid Stimulating Hormone (TSH) to include reflex T3 and T4 if abnormal.
- CA 19-9 (or CA 125, or CEA if not expressers of CA 19-9)
- Urinalysis
- Serum pregnancy test for women of childbearing potential
- Concomitant medications (past 30 days)
- Obtain archived tissue samples
- Patient to complete MDASI-GI and BPI questionnaires
- Distribute stool sample collection kit for exploratory microbiome and mycobiome analysis
    - **Note:** the stool sample needs to be returned to the site within 72 hours of collection.

Once eligibility is confirmed, site personnel will be provided a patient ID by HonorHealth.

5.5 On-Study Assessments

Patients must begin Cycle 1 within 21 days of signing the informed consent document and after the screening assessments. Treatment will be administered by qualified and trained site personnel in a hospital, clinic, or other out-patient setting appropriate for chemotherapeutic infusions. Each cycle is 42 days long and each visit has a window of +/- 24 hours.

Day 1 of each cycle – all assessments completed prior to dosing must be completed 72 hours prior to dosing.

- Review inclusion and exclusion criteria
- Directed physical examination including weight (kg)
- Karnofsky Performance Status (KPS) (see Appendix B)
- Vital signs (blood pressure, pulse, respiratory rate, and temperature)
- Adverse Events
- Body Surface Area (BSA) Calculation
- Complete blood count (CBC) with differential and platelet count
- Serum chemistries (for hepatic and renal function tests) including blood urea nitrogen (BUN), phosphorus, magnesium, creatinine, creatinine clearance, total protein, albumin, calcium, glucose, total bilirubin, alkaline phosphatase (ALP), aspartate aminotransferase (AST), alanine aminotransferase (ALT), and electrolytes (chloride, sodium, potassium, and bicarbonate)
- Thyroid Stimulating Hormone (TSH) to include reflex T3 and T4 if abnormal.
- CA 19-9 (or CA 125, or CEA if not expressers of CA 19-9)
- Collect blood sample for exploratory biomarker assays
- Urinalysis
- Serum pregnancy test for women of childbearing potential
- Concomitant medications
- Administer Nivolumab (as per dosing guidelines)
- Administer Albumin-Bound Paclitaxel (as per dosing guidelines)

- Administer Cisplatin (as per dosing guidelines)
- Administer Gemcitabine (as per dosing guidelines)
- Administer Paricalcitol (as per dosing guidelines)
- Patient to complete MDASI-GI and BPI questionnaires

Day 2, 9, 23 and 30 of each cycle – all assessments completed prior to dosing must be completed 24 hours prior to dosing.

- Provide optional IV fluids if necessary
- Administer pegfilgrastim (Neulasta®) on Days 9 and 30
- Adverse Events
- Concomitant medications

Day 4, 12, 18, 26, 32, 36 and 39 of each cycle – all assessments completed prior to dosing must be completed 24 hours prior to dosing.

- Administer Paricalcitol (as per dosing guidelines)
- Adverse Events
- Concomitant medications
- Complete blood count (CBC) with differential and platelet count (Day 36 only)
- Serum chemistries (for hepatic and renal function tests) including blood urea nitrogen (BUN), phosphorus, magnesium, creatinine, creatinine clearance, total protein, albumin, calcium, glucose, total bilirubin, alkaline phosphatase (ALP), aspartate aminotransferase (AST), alanine aminotransferase (ALT), and electrolytes (chloride, sodium, potassium, and bicarbonate) (Day 36 only)
- Distribute stool sample collection kit for exploratory microbiome and mycobiome analysis (Day 39 only)
    - **Note:** the stool sample needs to be returned to the site within 72 hours of collection.

Day 8 of each cycle – all assessments completed prior to dosing must be completed 24 hours prior to dosing.

- Directed physical examination including weight (kg)
- Karnofsky Performance Status (KPS) (see Appendix B)
- Vital signs (blood pressure, pulse, respiratory rate, and temperature)
- Adverse Events
- Complete blood count (CBC) with differential and platelet count
- Serum chemistries (for hepatic and renal function tests) including blood urea nitrogen (BUN), phosphorus, magnesium, creatinine, creatinine clearance, total protein, albumin, calcium, glucose, total bilirubin, alkaline phosphatase (ALP), aspartate aminotransferase (AST), alanine aminotransferase (ALT), and electrolytes (chloride, sodium, potassium, and bicarbonate)
- Concomitant medications
- Administer Albumin-Bound Paclitaxel (as per dosing guidelines)
- Administer Cisplatin (as per dosing guidelines)
- Administer Gemcitabine (as per dosing guidelines)
- Administer Paricalcitol (as per dosing guidelines)
- Patient to complete MDASI-GI and BPI questionnaires

Day 15 of each cycle – all assessments completed prior to dosing must be completed 24 hours prior to dosing.

- Directed physical examination including weight (kg)
- Karnofsky Performance Status (KPS) (see Appendix B)
- Vital signs (blood pressure, pulse, respiratory rate, and temperature)
- Adverse Events
- Complete blood count (CBC) with differential and platelet count
- Serum chemistries (for hepatic and renal function tests) including blood urea nitrogen (BUN), phosphorus, magnesium, creatinine, creatinine clearance, total protein, albumin, calcium, glucose, total bilirubin, alkaline phosphatase (ALP), aspartate aminotransferase (AST), alanine aminotransferase (ALT), and electrolytes (chloride, sodium, potassium, and bicarbonate)
- Concomitant medications
- Administer Nivolumab (as per dosing guidelines)
- Administer Paricalcitol (as per dosing guidelines)
- Patient to complete MDASI-GI and BPI questionnaires

Day 22 of each cycle – all assessments completed prior to dosing must be completed 24 hours prior to dosing.

- Directed physical examination including weight (kg)
- Karnofsky Performance Status (KPS) (see Appendix B)
- Vital signs (blood pressure, pulse, respiratory rate, and temperature)
- Adverse Events
- Body Surface Area (BSA) Calculation
- Complete blood count (CBC) with differential and platelet count
- Serum chemistries (for hepatic and renal function tests) including blood urea nitrogen (BUN), phosphorus, magnesium, creatinine, creatinine clearance, total protein, albumin, calcium, glucose, total bilirubin, alkaline phosphatase (ALP), aspartate aminotransferase (AST), alanine aminotransferase (ALT), and electrolytes (chloride, sodium, potassium, and bicarbonate)
- CA 19-9 (or CA 125, or CEA if not expressers of CA 19-9)
- Thyroid Stimulating Hormone (TSH) to include reflex T3 and T4 if abnormal.
- Urinalysis
- Serum pregnancy test for women of childbearing potential
- Concomitant medications
- Administer Albumin-Bound Paclitaxel (as per dosing guidelines)
- Administer Cisplatin (as per dosing guidelines)
- Administer Gemcitabine (as per dosing guidelines)
- Administer Paricalcitol (as per dosing guidelines)
- Patient to complete MDASI-GI and BPI questionnaires

Day 29 of each cycle – all assessments completed prior to dosing must be completed 24 hours prior to dosing.

- Directed physical examination including weight (kg)
- Karnofsky Performance Status (KPS) (see Appendix B)
- Vital signs (blood pressure, pulse, respiratory rate, and temperature)

- Adverse Events
- Complete blood count (CBC) with differential and platelet count
- Serum chemistries (for hepatic and renal function tests) including blood urea nitrogen (BUN), phosphorus, magnesium, creatinine, creatinine clearance, total protein, albumin, calcium, glucose, total bilirubin, alkaline phosphatase (ALP), aspartate aminotransferase (AST), alanine aminotransferase (ALT), and electrolytes (chloride, sodium, potassium, and bicarbonate)

- Concomitant medications
- Administer Nivolumab (as per dosing guidelines)
- Administer Albumin-Bound Paclitaxel (as per dosing guidelines)
- Administer Cisplatin (as per dosing guidelines)
- Administer Gemcitabine (as per dosing guidelines)
- Administer Paricalcitol (as per dosing guidelines)
- Patient to complete MDASI-GI and BPI questionnaires

At the end of each cycle and before the next cycle begins, the following will be completed:

- CT/MRI tumor assessment
- Reassessment of the extent of tumor should be made by the same imaging methods used to establish baseline tumor measurements. When a CR is documented, a confirmatory FDG PET scan will be obtained.
- In order to more precisely determine time to progression, the investigator is encouraged to obtain radiological assessments earlier if there is a strong clinical suspicion of disease progression, in order to either confirm or refute the clinical impression.
- Patients who have not had any disease progression at the end of cycle 4 may be considered for Continuation Therapy.

5.6 End of Study

When the patient completes all cycles of study medication, or withdraws from treatment prior to completing all cycles, the following assessments will be performed 14-28 (+/- 2) days after completing the last dose of study treatment:

- Directed physical examination including weight (kg)
- Karnofsky Performance Status (KPS) (see Appendix B)
- Vital signs (blood pressure, pulse, respiratory rate, and temperature)
- Adverse Events
- Complete blood count (CBC) with differential and platelet count
- Serum chemistries (for hepatic and renal function tests) including blood urea nitrogen (BUN), phosphorus, magnesium, creatinine, creatinine clearance, total protein, albumin, calcium, glucose, total bilirubin, alkaline phosphatase (ALP), aspartate aminotransferase (AST), alanine aminotransferase (ALT), and electrolytes (chloride, sodium, potassium, and bicarbonate)
- Coagulation panel including PTT and PT/INR
- Thyroid Stimulating Hormone (TSH) to include reflex T3 and T4 if abnormal.
- Concomitant medications
- Patient to complete MDASI-GI and BPI questionnaires

5.7 Follow-Up Assessments after End of Study or Early Termination

Follow-up assessments by telephone will be conducted for all patients every 12 weeks, start 12 weeks after the last dose of study treatment, to determine the patient's vital status, and date of death if applicable.

5.8 Treatment Assignment

This is a phase II open-label pilot trial, with the identity of the treatment known to the patients, Investigators, drug provider, and CRO.

5.9 Patient Disposition

Summaries of patient disposition will include:

- Patient discontinuation from treatment.
- Patient discontinuation from study
- Overall qualification status of all patients.

All patients enrolled in the study will be included in the summation. The safety population will include all patients who have received at least one dose of any study drug. The number of patients who do not qualify for analysis, who die or discontinue before treatment begins, will be summarized.

5.10 Patient Characteristics

Patient characteristics will include a summary of the following:

- Patient demographics
- Baseline disease characteristics
- Pre-existing conditions
- Prior therapies
- Concomitant medications and treatments

Other patient characteristics will be summarized as appropriate.

5.11 Statistical Considerations

The sample size of this pilot study will be 10 patients and if a partial response rate is noted in ≥ 4 patients then the study size can be increased up to 25 patients. This is based on a test of a null hypothesis of a 5% partial response or less, versus an alternative hypothesis of a 30% partial response rate or greater. Four or more partial responders in 10 will be required in order

to proceed to the total enrollment of 25 patients. Eight or more partial responders out of 25 patients will be sufficient evidence for rejection of the null hypothesis of insufficient activity of the regimen. This design has a power of 87% at a one-sided Type I error rate of 3%.

Time-to-event endpoints, including PFS and OS will be assessed using the Kaplan-Meier method (Kaplan 1958). QOL instruments will both be assessed utilizing descriptive statistics (Means and SDs for the individual symptom and interference items) will be used to summarize patient responses. Longitudinal data will be examined and mean symptom severity and interference will be compared using descriptive analysis and *t*-tests (repeated measures).

Objective response rates, clinical benefit response, and CA 19-9, will be summarized descriptively.

5.12 Efficacy Analysis

The efficacy analysis will include summaries for the following parameters: complete response rate (CR) (see section 6.11), objective response rate (CR + PR), disease control rate (CR + PR + SD at 12 weeks), progression-free survival (PFS), stable disease rate at 12 weeks (SD), and overall survival (OS). The efficacy analysis will only be conducted on patients who have received at least one dose of nivolumab, albumin-bound paclitaxel, paricalcitol, cisplatin, gemcitabine and have at least one post baseline tumor assessment.

Objective responses will be evaluated using the Response Evaluation Criteria in Solid Tumors 1.1 (RECIST 1.1). Changes (i.e. improvements) in tumor measurements from baseline values will be assigned a status of CR or PR or SD. Objective response measurements will comprise the sum of CR plus PR. The overall response rate, as well as the rates for the individual categories of response (i.e. CR, PR, SD, and PD), will be estimated by the percentage of patients achieving these criteria. The disease control rate will consist of the sum of CR + PR + SD for 12 weeks. When a CR is documented, a confirmatory PET scan will be obtained.
For the estimation of progression-free and overall survival, a Kaplan-Meier analysis will be performed.

Progression-free survival is defined as the interval from the date of registration (i.e. assignment of patient number) to the earliest date of documented evidence of recurrent or progressive disease, or the date of death due to any cause, whichever occurs first. Patients who do not progress and remain alive will be censored at their last radiographic assessment date.
Overall survival will be measured from the date of registration (i.e. assignment of patient number) to the date of death due to any cause, or the date of last contact (censored observations).

5.13 Safety Analysis

All patients who receive any amount of nivolumab, albumin-bound paclitaxel, paricalcitol, cisplatin, or gemcitabine will be included in the following safety analyses:

- The incidence, severity, duration, causality, seriousness, and type of AEs
- Changes in the patient's physical examination, vital signs, and clinical laboratory results
- Grading of clinical laboratory results per CTCAE criteria for selected laboratory parameters
- Deaths

- Concomitant medications

5.14 Replacement of Patients

Patients who are enrolled into the study, but fail to receive nivolumab, albumin-bound paclitaxel, paricalcitol, cisplatin, and gemcitabine may be replaced.

6 EVALUATION OF RESPONSE

6.1 Best Overall Response

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

6.2 Overall Tumor Response

The overall tumor response rate is defined as the total proportion of patients who have an objective tumor response (CR + PR). Rates for the individual categories of response (CR, PR, SD, and PD) will also be determined.

6.3 Not Evaluable

Patients will be defined as being not evaluable for response if a post-baseline radiological assessment cannot be made. These patients will be counted as treatment failures in the analysis of tumor response data.

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

6.4 Progression-free Survival

Progression-free survival (PFS) is defined as the time from enrollment (i.e. assignment of patient ID number) to first documentation of objective tumor progression or to death due to any cause. Patients who do not progress and remain alive will be censored at the date of their last tumor assessment.

6.5 Survival

Survival is defined as the time from enrollment (i.e. assignment of patient ID number) to date of death. In the absence of confirmation of death, survival time will be censored at the last date the patient is known to be alive.

6.6 Analysis Plan

Continuous variables will be summarized using the mean (SD) or median (range). Frequency tables will be used to summarize categorical variables. The distribution of time-to-event endpoints (e.g. response duration, progression-free survival, overall survival) will be estimated using the Kaplan and Meier method. Cox (proportional hazards) regression may be used to evaluate multivariable predictive models of time-to-event outcomes. Additional details regarding statistical analyses will be presented in a Statistical Analysis Plan.

6.7 Guidelines for Measuring Disease

Antitumor activity will be evaluated by RECIST 1.1 criteria (Eisenhauer 2009). These response criteria are widely recognized and accepted as the standard criteria for determining response in patients with solid tumors.

6.8 Disease Definitions

Measurable disease is defined as the presence of ≥1 measurable lesion. If the measurable disease is restricted to a solitary lesion, its neoplastic nature should be confirmed by cytology/histology.

At Baseline, tumor lesions will be categorized as:

Measurable Lesions: lesions that can be accurately measured in at least one dimension (longest diameter in the plane of measurement is to be recorded) with a minimum size of:

- 10 mm by CT scan (CT scan slice thickness no greater than 5 mm)
- 10 mm caliper measurement by clinical exam (lesions which cannot be accurately measured with calipers should be recorded as non-measurable)
- 20 mm by chest X-ray

Malignant lymph nodes: to be considered pathologically enlarged and measureable, a lymph node must be ≥15 mm in ***short*** axis when assessed by CT scan (CT scan slice thickness recommended to be no greater than 5 mm). At Baseline and follow-up, only the ***short*** axis will be measured and followed.

OR

Non-measurable Lesions: all other lesions, including small lesions (longest diameter <10 mm or pathological lymph nodes with ≥10 to <15 mm short axis) as well as truly non-measurable lesions. Lesions considered truly non-measurable include: leptomeningeal disease, ascites, pleural/pericardial effusion, inflammatory breast disease, lymphangitis cutis/pulmonis, abdominal masses/abdominal organomegaly identified by physical exam that is not measurable by reproducible imaging techniques.

For special considerations regarding lesion measurability for bone lesions, cystic lesions and lesions with prior local treatment, consult the RECIST 1.1 guidelines in the Study Manual.

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

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

Clinical lesions will only be considered measurable when they are superficial (e.g. skin nodules and palpable lymph nodes). For the case of skin lesions, either a CT scan or documentation by color photography, including a ruler to estimate the size of the lesion, is to be done.

6.9 Methods of Measurement

Tumor measurements should be performed using the same method as well as the same staff member per patient, if possible, throughout the study. CT and MRI are the best currently available and reproducible methods to measure target lesions selected for response assessment. Conventional CT and MRI should be performed with cuts of ≤5 mm in slice thickness contiguously. This applies to tumors of the chest, abdomen, and pelvis.
As a rule, the minimum size of the lesion should be no less than double the slice thickness. Lesions on chest x-rays are acceptable as measurable lesions when they are clearly defined and surrounded by aerated lung. However, CT is preferable.

Ultrasound should not be used to measure tumor lesions. It is, however, a possible alternative to clinical measurements of superficial palpable lymph nodes, subcutaneous lesions, and thyroid nodules. Ultrasound might also be useful to confirm the complete disappearance of superficial lesions usually assessed by clinical examination. If new lesions are identified by ultrasound in the course of the study, confirmation by CT or MRI is necessary.

Tumor markers *alone* cannot be used to assess objective tumor response. If markers are initially above the upper normal limit, they must normalize for a patient to be considered in complete clinical response.

Cytology and histology can be used to differentiate between partial response (PR) and complete response (CR) in rare cases (e.g. after treatment to differentiate between residual benign lesions and residual malignant lesions in tumor types such as germ cell tumors) if required by protocol.

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

Target Lesions: all measurable lesions up to a maximum of 2 lesions per organ and 5 lesions in total, representative of all involved organs will be identified as target lesions and will be recorded and measured at baseline. Target lesions should be selected on the basis of their size (lesions with the longest diameter [LD]), be representative of all involved organs, and their suitability for accurate repetitive measurements (either by imaging techniques or clinically). A sum of the LD for all target lesions will be calculated and reported as the baseline sum LD. The baseline sum of the LD will be used as reference to further characterize the objective tumor response.

Non-target Lesions: all other lesions (or sites of disease) including pathological lymph nodes should be identified as non-target lesions and will also be recorded at baseline. Measurements

of these lesions are not required, but the presence or absence of each should be noted throughout follow-up.

6.11 Response Criteria

Table 7 RECIST Target Lesion Response Criteria

Target Response Criteria	Definition
Complete Response (CR)	The disappearance of all target lesions and no new sites or disease-related symptoms confirmed at least 4 weeks after initial documentation. Any pathological lymph nodes (whether target or non-target) must have a reduction in short axis to < 10 mm. All sites must be assessed, including non-measurable sites, such as effusions, or markers.
Partial Response (PR)	At least a 30% decrease in the sum of the diameters of target lesions, taking as a reference the baseline sum of the diameters confirmed at least 4 weeks after initial documentation. PR is also recorded when all measurable disease has completely disappeared, but a non-measurable component (i.e., ascites) is still present but not progressing.
Stable Disease (SD)	Neither sufficient shrinkage to qualify for partial response nor sufficient increase to qualify for progressive disease.
Progressive Disease (PD)	At least a 20% increase in the sum of the diameters of target lesions, taking as reference the smallest sum of the diameters recorded since on study (this includes the baseline sum if that is the smallest on study), which must also demonstrate an absolute increase of at least 5 mm; or the appearance of one or more new lesions.

Table 8 RECIST Non-target Lesion Response Criteria

Non-Target Response Criteria	Definition
Complete Response (CR)	Disappearance of all non-target lesions and normalization of tumor marker level confirmed at least 4 weeks after initial documentation. All lymph nodes must be non-pathological in size (< 10 mm short axis).
Non-Complete Response/ Non- Progressive Disease (Non-CR/Non-PD)	Persistence of one or more non-target lesions and/or the maintenance of tumor marker level above the normal limits.
Progressive Disease (PD)	Appearance of one or more non-target lesions and/or unequivocal progression of existing non-target lesions (“unequivocal progression” is defined as an overall level of substantial worsening in non-target disease that is of magnitude that, even in the presence of SD or PR in target disease, the treating physician would feel it important to change therapy).

Non-target lesion response will be classified according to the RECIST Non-Target Lesion Response Criteria in the following table.

6.12 Evaluation of Best Overall Response

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

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

In some circumstances, it may be difficult to distinguish residual disease from normal tissue. When the evaluation of complete response depends on this determination, it is recommended that the residual lesion be investigated (fine needle aspirate/biopsy) to confirm the complete response status.

Table 9 Immune-Related RECIST Response Criteria

Response Criteria	Definition
irCR	Complete disappearance of all lesions (whether measurable or not, and no new lesions, and confirmation by a repeat consecutive assessment no less than 4 weeks from date first documented
irPR	Decrease in tumor burden >50% relative to baseline confirmed by repeat consecutive assessment at least 4 weeks later
irSD	Not meeting criteria for irCR or irPR in absence of ir PD
irPD	Increase in tumor burden >25% relative to nadir (minimum recorded tumor burden) confirmed by repeat consecutive assessment at least 4 weeks later

Table 10 RECIST Overall Response Criteria

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

NE – Non-evaluable

6.13 Duration of Stable Disease

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

For the purposes of this Trial, the minimal time interval required between 2 measurements for determination of SD is 6 weeks (at least 2 consecutive assessments 6 weeks apart revealing SD). This time interval takes into account the expected clinical benefit that such a status may bring to the population under study.

7 SAFETY

The investigator is responsible for monitoring the safety of patients who have enrolled in the study. All adverse events (AEs) occurring after any administration of the study medication will be followed until the event resolves, until the patient begins alternative treatment, or until the end of the study. Investigators will grade AEs using the NCI CTCAE, version 4.0 (published 28 May 2009) (see 0).

Investigators are required to document all Grades of AEs (Grades 1, 2, 3 or 4) occurring during the clinical trial, commencing with the first dose of study medication and including the protocol-defined post-treatment follow-up period (21 CFR §312.64[b]) on designated CRF pages. All Grades of AEs occurring following the signature of the informed consent, but prior to the first dose of study drug, will not be reported as AEs. It is also important to record all AEs that result in permanent discontinuation of the investigational product being studied, whether serious or non-serious.

Serious adverse events (SAEs), as defined below, must be reported to HonorHealth or its representative within 24 hours of knowledge of their occurrence. An independent Data Safety and Monitoring Committee (DSMC) will review all AEs and SAEs to ensure patient safety. See section 8.1.4 for further details.

7.1 Adverse Events

An AE is any unfavorable medical occurrence in a clinical investigation patient administered a pharmaceutical product, which does not necessarily have to have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign, symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not considered related to the medicinal (investigational) product. All Grade 3 and 4 AEs, including observed or volunteered problems, complaints, or symptoms, are to be recorded on the CRF. Each AE is to be evaluated for duration, intensity, and causal relationship with the study medication or other factors. All Grade AEs that are considered related to the study treatment regimen must be followed to resolution or stabilization if improvement is not expected. Progression of disease is considered an efficacy outcome parameter and should not be captured as an AE.

A non-serious AE is any untoward medical occurrence that does not meet any of the criteria for SAEs.

Patients should be instructed to report any AE that they experience to the Investigator, starting from the time of their first dose. Investigators should assess AEs at each visit. All grades of AEs occurring during the clinical trial, starting at the time of the initial study drug infusion, and the follow-up period should be recorded on the appropriate AE page of the CRF.

Wherever possible, a specific disease or syndrome rather than individual associated signs and symptoms should be identified by the investigator and recorded on the CRF. However, if an observed or reported sign or symptom is not considered a component of a specific disease or syndrome by the investigator, it should be recorded as a separate AE on the CRF.

7.2 Serious Adverse Events

A serious adverse event (SAE) is any adverse experience occurring at any dose that results in any of the following outcomes:

- Death
- A life-threatening adverse event
- Life-threatening is defined as an event with immediate risk of death from the event as it occurred. It does not include an event that might have caused death if it occurred with a greater severity.
- In-patient hospitalization or prolongation of existing hospitalization
- Results in a persistent or significant disability/incapacity
- A congenital anomaly/birth defect
- Important medical events that may not be immediately life-threatening, or result in death or hospitalization, but may jeopardize the patient or may require intervention to prevent one of the other listed outcomes above.
  .

7.3 Adverse Event Severity

AE will be graded according to the NCI CTCAE, Version 4.0 (see 0)

- Grade 1 Mild AE: asymptomatic or mild symptoms. Clinical intervention not indicated
- Grade 2 Moderate AE: Minimal local or noninvasive intervention indicated
- Grade 3 Severe AE: Severe or medically significant but no immediately life-threatening hospitalization or prolongation of hospitalization indicated; the event is disabling;
- Grade 4 Life-threatening or disabling AE: urgent intervention indicated;

- Grade 5 Death related to AE

Severity versus Seriousness: Severity is used to describe the intensity of a specific event while the event itself, however, may be of relatively minor medical significance (such as severe headache). This is not the same as "seriousness," which is based on patient/event outcome at the time of the event. For example, the NCI CTCAE grade 4 (life-threatening or disabling AE) is assessed based on unique clinical descriptions of severity for each AE, and these criteria may be different from those used for the assessment of AE seriousness. An AE assessed as grade 4 based on the NCI CTCAE grades may or may not be assessed as serious based on the seriousness criteria.

7.4 Causality Assessment

The relationship of an AE to the study drug must be classified as one of the following:

- **Unrelated:** The AE is clearly not related to the study medication;
- **Unlikely Related:** It is doubtful that the AE is related to study medication;
- **Possibly Related:** The AE may be related to the study medication;
- **Probably Related:** The AE is likely related to the study medication;
- **Definitely Related:** The AE is clearly related to the study medication;

7.5 Safety and Tolerance Analysis

The incidence of all AEs (regardless of causality) and all treatment-related AEs (those AEs thought to be possibly, probably, or definitely related to study drug) will be summarized by NCI CTCAE Version 4.0 term and maximum grade. The incidence of SAEs and AEs that lead to discontinuation of study drug will also be summarized. Listings of patients who discontinue study drug due to an AE and patients with SAEs and deaths will be presented. Narratives will be provided for patients who experience an SAE.

7.5.1 Laboratory Assessments

7.5.1.1 Hematology Parameters

To investigate the maximal degree of myelosuppression, the NCI CTCAE Version 4.0 grade for WBC, ANC, platelet count, and hemoglobin concentration will be summarized by the most severe grade in the first treatment cycle and by the most severe grade during the therapy for each treatment group; testing of treatment group differences will be performed using a CMH test. The incidence of patients with NCI CTCAE Version 4.0 hematology values of All AE Grades that occurred after the first dose of study drug will be presented. Data for patients with Grades, 1, 2, 3 or 4 hematology values will be listed.

7.5.1.2 Clinical Chemistry

Liver and renal function will be summarized using the NCI CTCAE Version 4.0 for alkaline phosphatase, ALT, AST, total bilirubin, BUN and creatinine. The number and percentage of

patients who have more than one NCI CTCAE Version 4.0 grade will be summarized using the most severe Grade for the first cycle of therapy and for anytime during therapy for each treatment group; testing of treatment group differences will be performed using a Cochran-Mantel-Hanzel test. The incidence of patients with NCI CTCAE Version 4.0 chemistry values of Grade 1, 2, 3 or 4 that occurred after the first dose of study drug will be presented. Data for patients with Grade 1, 2, 3 or 4 chemistry values will be listed.

7.5.2 Peripheral Neuropathy

Peripheral neuropathy events will be captured according to protocol and reported by Investigators and investigative staff in accordance with adverse event and SAE reporting standards.

7.6 Patient Reporting of AEs and SAEs

Patients are to be encouraged to call the site to report any unexpected symptoms or problems they encounter between office visits. These events should be considered in the same fashion as if they had been reported at a scheduled office visit. At each scheduled office visit, after the patient has had an opportunity to spontaneously mention any problems, the Investigator should inquire about AEs by asking the following standard questions

- Have you had any (other) medical problems since your last clinic visit?
- Have you taken any new prescribed or over-the-counter medicines or herbal/vitamin preparations, other than those given to you in this study, since your last visit/assessment?
- Have any new procedures been performed since your last study visit?

7.7 Investigator Reporting Serious Adverse Events

The Investigator is responsible for notifying the appropriate health authorities (HAs), ethics committees (ECs), and other investigators, of any expedited, annual, or other periodic safety reports in accordance with applicable regulations. The Investigator is also responsible for notifying the local ECs in accordance with local regulations. Reporting will be coordinated through HonorHealth Research Institute Administration. Generally, Expedited Safety Reports are required for all SAEs that are assessed to be unexpected and possibly, probably or definitely related to study drug(s), as specified ICH EG Good Clinical Practices. However, certain Regulatory Agencies may have additional requirements for expedited safety report submissions.

The Investigator is responsible for recording, reporting and following all Grade 1,2, 3 or 4 AEs, regardless of causality, observed during the study period, starting with initial dose of study drug and ending at the time the patient goes off study or 30 days after patient's last dose of study drug, whichever is later. The Investigator should follow AEs until the event is resolved or stabilized, the patient is lost to follow-up, or the event is otherwise explained. Events occurring within 30 days prior to study drug administration should be recorded as pre-treatment signs and symptoms. The only exception to this is for an AE that occurs prior to the first dose of study drug but is due to a procedure associated with assessments carried out to determine eligibility or to

permit participation in this protocol – this should be recorded as an AE (rather than a pre-treatment sign or symptom).

The Investigator or designee must completely and promptly record each AE in the source documentation, regardless of relationship to study drug as determined by the Investigator. Grade 1, 2, 3 and 4 AEs must be recorded in the CRF. **The Investigator must assess AE/SAE causality for any patients treated at his/her site and for any patients treated under the direct care of his/her sub-Investigators.** The Investigator should attempt, if possible, to establish a diagnosis based on the patient's signs and symptoms. When a diagnosis for the reported signs or symptoms is known, the Investigator should report the diagnosis, not the symptoms, as the AE.

Clinically significant laboratory abnormalities present at the initial treatment visit will be recorded as pre-treatment signs and symptoms.

All Grades (Grade 1, 2, 3 or 4) of adverse events and SAEs should be reported on the appropriate case report forms. **In addition, all SAEs must be reported promptly to HonorHealth after the Investigator recognizes/classifies the event as a SAE.** The specific reporting time frame depends on the type of SAE. For life-threatening or fatal events, the Investigator must report initial information on the SAE within 24 hours/ 1 business day of becoming aware of the event, preferably by fax or alternatively by phone or email; at a minimum, a description of the event and the Investigator's judgment of causality must be provided at the time of the initial report. If an SAE is reported by phone or by e-mail, the Investigator must fax a completed SAE report form to HonorHealth within 1 business days. The Investigator should follow all AEs/SAEs observed during the study until they resolve or stabilize, the patient is lost to follow-up, or the events are otherwise explained. The HonorHealth Drug Safety Team is responsible for notifying the relevant regulatory authorities and Bristol Myers Squibb of certain Serious Adverse Events.

For any additional questions regarding reporting requirements of a SAE, please contact the following individual:

HonorHealth Drug Safety Team

After hours, weekends, holidays: 480-323-1350

Business hours phone: 480-323-1323

E-mail: DrugSafety@honorhealth.com

7.7.1 Expedited Reporting by Investigator to HonorHealth

Serious adverse events (SAE) are defined above. The Investigator must inform HonorHealth in writing of any SAE within 24 hours (for life threatening or fatal event) of being aware of the event. The date of awareness should be noted on the report. This must be documented on a HonorHealth Drug Safety Reporting Form.

This form must be completed and supplied to HonorHealth Research Institute within 24 hours/ 1 business day at the latest on the following working day. The initial report must be as complete as possible, including details of the current illness and (serious) adverse event, and an assessment of the causal relationship between the event and the investigational product(s).

Information not available at the time of the initial report (e.g., an end date for the adverse event or laboratory values received after the report) must be documented on a follow-up HonorHealth Research Institute Reporting Form. A final report to document resolution of the SAE is required. The Study protocol number NAPPCG-EB 2015-001) and the institutional protocol number should be included on SAE reports to P HonorHealth Research Institute. A copy of the fax transmission confirmation of the SAE report or copy of email sent to HonorHealth Research Institute should be attached to the SAE and retained with the patient records.

7.7.2 IRB Notification of SAEs

The Investigator is responsible for promptly notifying the IRB of all SAEs, including any follow-up information, occurring at his/her site and any SAE regulatory reports and Investigational New Drug Safety Reports that he/she receives from HonorHealth Drug Safety.

7.8 SAE Follow-Up

For all SAEs occurring after first dose of study medication or within 100 days of the last administration of study medication, the investigator must submit follow-up reports to HonorHealth or its representative regarding the status of the SAE and the patient's subsequent course until the SAE has subsided, or until the condition stabilizes (in the case of persistent impairment), the patient receives alternative therapy, or the patient dies.

7.8.1 Sponsor Notification of Post-Study SAEs

The Investigator should notify HonorHealth of any new SAEs occurring within 30 days after a patient has withdrawn from the study and/or after the last study treatment if the SAE is determined to be related or possibly to the study medication used in the study. Additional information regarding any ongoing SAE determined to be related or possibly to the study medication used in the study should be reported to the Sponsor after the first telephone call to assess survival status that is conducted at 12 weeks after the last study treatment. Any information collected at these timepoints will be reported to Bristol-Myers Squibb if the SAE is determined to be related or possibly to treatment with Nivolumab. However, Investigators are not obligated to actively seek AEs in former study participants.

7.9 Pregnancy

While not considered a SAE unless a serious criterion is met, pregnancies occurring in patients enrolled on the study or in their partners must be reported. The investigator should complete the pregnancy report form and fax it to HonorHealth within 24 hours of knowledge of the pregnancy. Male and female subjects will be required to use contraception while receiving study medication and for 5 months after the last dose is given. Any pregnancies that occur, whether a female subject participating in the study or a partner of a male subject participant, will need to be reported to the Sponsor while the subject is receiving study medication and for 5 months after the last dose is given.

8 ETHICAL, LEGAL, AND ADMINISTRATIVE ASPECTS

8.1 Ethics

8.1.1 Institutional Review Board/ Ethics Committee Approval

Before study initiation, this protocol and informed consent form will be submitted for review and approval to the IRBs charged with oversight for the clinical sites. In addition, any form of proposed advertising and advertising text for patient recruitment must be reviewed and approved by HonorHealth prior to submission to the IRB. The Investigator will forward to HonorHealth or Sponsor-nominated designee a copy of the IRB's approval of this protocol, any amendments, informed consent form, and any modifications to the informed consent, based on the FDA regulations set forth in 21 CFR 56 of the *Code of Federal Regulations,* as well as those of the applicable regulatory bodies in all other participating countries outside of the U.S.
In addition, the Investigator will be responsible for forwarding to HonorHealth or Sponsor-nominated designee a description of the IRB board members (including profession and affiliation) or a United States (US) Department of Health and Human Services (DHHS) General Assurance number and expiration date. If neither of these is available, the chairperson must submit a statement indicating that the members of the board responsible for the review meet FDA and other appropriate regulatory requirements. In addition, the labeling for all approved study drugs should be submitted to the IRB for informational purposes.
Clinical supplies will not be shipped to the clinical site until IRB approval is obtained for the protocol. Any existing amendments, informed consent, and photocopies of the approved documents must be received by HonorHealth or other sponsor-nominated designee prior to drug shipment.

8.1.2 Ethical Conduct of the Study

This study will be conducted in compliance with the protocol, Good Clinical Practice (GCP), Guidelines of the International Conference on Harmonization (ICH) of Technical Requirements for Registration of Pharmaceuticals for Human Use, and in full compliance with the World Medical Association Declaration of Helsinki and its most recent amendments.

8.1.3 Informed Consent

Written informed consent of the patient to participate in the study must be obtained and documented by the Investigator in accordance with the FDA regulations set forth in 21 CFR 50 as well as the applicable regulatory bodies in all other participating countries outside the United States.

The Investigator must provide the patient with a copy of the informed consent form in a language understandable to the patient. Written consent should be obtained before any protocol-required procedures are performed, including any procedure not part of normal patient care (e.g., withdrawal of current medications).

Changes made by a participating site to the recommended informed consent must be must be forwarded to HonorHealth for approval prior to submission to the corresponding IRB. A copy of the signed informed consent will be given to the patient or their legal representative and a copy must be retained in the Investigator's study records.

8.1.4 Data Safety and Monitoring Committee

An independent Data Safety and Monitoring Committee (DSMC) will be formed to evaluate the safety and effectiveness of the study medication for each subject as well as study conduct of

each site. The DSMC will also review all SAEs reported by each site. The DSMC will review study data to determine if endpoints are being met and if the study can continue with or without changes to the protocol or if the study should be terminated immediately due to safety concerns or lack of data to support study endpoints. Findings and recommendations of the DSMC will be reported to the Sponsor after each meeting. The DSMC will meet on a quarterly basis or more frequently as needed if safety concerns are raised. Furthermore, prior to the expansion from 10 to 25 patients in the trial a review by the DSMC will be conducted. This treatment regimen combines 2 chemotherapeutic agents with known toxicity profiles, with a subsequent treatment of a combination of 3 chemotherapeutic agents with known toxicity profiles. Because cancer is a life-threatening disease, treatments that result in Grade 3 and 4 toxicities are considered to have an acceptable risk profile. Data reported to HonorHealth will be received by the Lead Principal Investigator on a regular basis and not less than once a month. In addition, SAEs will be reported to HonorHealth immediately and reviewed as they are received. Any unacceptable toxicities or severe toxicities that occur more frequently than expected will be discussed by the Lead Principal Investigator, the Medical Monitor, and the site Principal Investigators who will decide jointly whether the study should be modified, interrupted, or stopped. A monthly conference call will be held with investigators participating in the study. The statistical group will provide listings of toxicities on a regular basis.

8.2 Disclosure of Data

8.2.1 Study Data Monitoring Plan

HonorHealth ensures that appropriate monitoring procedures are performed before, during and after the study. Before the study is initiated at a site visit or at an investigator meeting, all aspects of the study are reviewed with the Investigator and the staff. Prior to enrolling patients into the study, a HonorHealth representative will review the protocol, CRFs, procedures for obtaining informed consent, record keeping, and reporting of AEs/SAEs with the Investigator. Monitoring will include on-site visits with the Investigator and study team as well as any appropriate communications by mail, email, fax, or telephone.

Data monitoring procedures will be carried out by HonorHealth for all participating sites, and will be performed on a regular basis to comply with Good Clinical Practice guidelines.

Review of the case report forms, cross-reference with source documentation (including radiology review), review of study related regulatory documents and logs (e.g., enrollment, study site staff, drug accountability), and review of drug accountability will be monitored on an ongoing basis during monitoring sessions. The monitor will ensure that the investigation is conducted according to protocol design and regulatory requirements.

At the conclusion of the monitoring visit, the site monitor will meet with the site staff to discuss and request specific corrections to the case report forms, and/or request clarification, and/or additional source documentation. The site Clinical Research Coordinator responsible for the study will be provided with a copy of the written monitoring notes for resolution of the findings. The HonorHealth site monitor will complete a written monitoring report and forward it to the site Principal Investigator and to HonorHealth Administration. The report will include a summary of what the site monitor reviewed and the site monitor's statements concerning the significant findings/facts, deviations and deficiencies, conclusions, actions taken or to be taken, and/or actions recommended to ensure compliance. The site Principal Investigator will be expected to submit any Corrective Action Plans, in writing, to HonorHealth Administration and the

HonorHealth site monitor. A copy of the monitoring forms, final monitoring reports, and Corrective Action Plan will be kept in the site monitor's study file at HonorHealth for follow-up at the next monitoring session.

8.2.2 Confidentiality

The Investigator and any other study personnel involved in this study shall not disclose, or use for any purposes (other than for the performance of this study), any data, records, or other information (hereinafter collectively "information") disclosed to the Investigator or other study personnel. Such information shall remain the confidential and proprietary property of HonorHealth, and shall be disclosed only to the Investigator or other designated study personnel.

The obligation of non-disclosure shall not apply to the following:

- relevant disclosure to potential study participants for the purpose of obtaining informed consent;
- information after such time that it is or becomes publicly available through no fault of the Investigator or other study personnel; and
- information after such time that it is disclosed to the Investigator by a third party entitled to disclose such information.

If the study site is a 'covered site' under the definitions of the Health Insurance Portability and Accounting Act (HIPAA), the Investigator will ensure that the patient consents to the use of data by HonorHealth and its designees for the purposes of regulatory submissions, study publications, and drug approval.

8.2.3 Publication

The Investigator(s) shall have the right, consistent with academic standards and with due regard to the protection of HonorHealth confidential information and intellectual property, to publish or present the results of work performed in accordance with the study; provided that any proposed publication or presentation is first reviewed and approved in writing by HonorHealth shall complete its review within 60 days after receipt of the proposed publication or presentation. Upon HonorHealth request, proposed publication or presentation will be delayed up to 60 additional days to enable HonorHealth to secure adequate intellectual property protection of property of HonorHealth that would be affected by such proposed publication or presentation. If HonorHealth believes in good faith that any proposed publication or presentation contains any confidential information and/or intellectual property HonorHealth shall have the right to remove references to any such confidential information and/or intellectual property.

8.3 Protocol Compliance

The investigator will conduct the study in compliance with the protocol given approval/favorable opinion by the IRB/IEC and the appropriate regulatory authority(ies). Changes to the protocol will require approval from HonorHealth, in addition to written IRB/IEC approval/favorable opinion prior to implementation, except when the modification is needed to eliminate an immediate hazard(s) to patients. The IRB/IEC may provide, if applicable regulatory authority(ies)

permit, expedited review and approval/favorable opinion for minor change(s) in ongoing studies that have the approval /favorable opinion of the IRB/IEC. The investigator will submit all protocol modifications to HonorHealth and the regulatory authority(ies) in accordance with the governing regulations. Any departures from the protocol must be fully documented in the source documents.

8.4 Quality Assurance

All aspects of the study will be carefully monitored by HonorHealth and/or its authorized representative for compliance with applicable government regulations with respect to current ICH GCP guidelines as well as other applicable regulations and guidelines.

8.5 On-site Audits

Regulatory authorities, the IEC/IRB, and/or HonorHealth may request access to all source documents, data capture records, and other study documentation for on-site audit or inspection. Direct access to these documents must be guaranteed by the investigator, who must provide support at all times for these activities.

8.6 Premature Closure of the Study

This study may be prematurely terminated, if in the opinion of the Lead Principal Investigator or HonorHealth there is sufficient reasonable cause.

HonorHealth has the right to discontinue the study under the conditions specified in the clinical Trials agreement. Written notification documenting the reason for study termination will be provided to the site investigator by the terminating party.

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

- Determination of unexpected, significant, or unacceptable risk to patients
- Failure to enter patients at an acceptable rate
- Insufficient adherence to protocol requirements
- Insufficient complete and/or evaluable data
- Plans to modify, suspend or discontinue the development of the drug
- Recommendation from the DSMC to close the study

Should the study be closed prematurely, all study materials must be returned to HonorHealth.

8.7 Investigator Documentation

8.7.1 Form FDA 1572

The Investigator must provide HonorHealth with a fully executed Form FDA 1572. Any updates must be provided via a new fully executed Form FDA 1572.

8.7.2 Curriculum Vitae

The Investigator must provide HonorHealth with his/her current signed and dated curriculum vitae and a current signed and dated curriculum vitae for each sub-Investigator listed on Form FDA 1572. Current signed and dated curriculum vitae is defined as updated within 2 years of study start up.

8.7.3 Financial Disclosures

The Investigator and sub-Investigator(s) must complete a Clinical Investigator Financial Certification/Disclosure Statement to report financial interests and arrangements that may be of concern to FDA per 21 CFR 54.

8.7.4 Laboratory Certification and Normal Ranges

The Investigator will indicate on the Form FDA 1572 the name and location of any local laboratories that will be used for laboratory assessments. The Investigator will provide a copy of all clinical laboratory certifications, certification numbers, dates of certifications, and a list of the normal ranges for all laboratory tests for all facilities listed. Updated versions of these documents must be provided to HonorHealth as appropriate. In the event the clinical laboratory is changed during the study, HonorHealth will be promptly notified, and the Form FDA 1572 will be updated. Appropriate documentation will be submitted to HonorHealth to verify the certification of the new laboratory.

All radiology facilities being utilized outside the investigative site must be pre-approved by HonorHealth, and included on the Form FDA 1572.

8.8 Records Retention

In accordance with applicable regulatory requirements, following closure of the study, the Investigator will maintain a copy of all site study records in a safe and secure location. HonorHealth will inform the Investigator of the time period for retaining these records in order to comply with applicable regulatory requirements.

HonorHealth reserves the right to terminate the study for refusal of the Investigator and/or investigational site to comply with any requirements stated in this study protocol.

8.9 Protocol Deviations

Deviations from the protocol must be addressed as protocol amendments with IRB approval required prior to implementation. Apart from the regulatory requirements, it is vital to the success of the study that the Investigator adheres to the details of the protocol and thus holds to a minimum the number of cases that may be later classified as “incomplete,” “unusable,” or “not evaluable.”

9 DATA MANAGEMENT

9.1 Patient Enrollment Instructions

Potential study participating screening packages will be submitted to Sponsor for review. If patient eligible for participation, Sponsor/designee shall assign subject ID and provide documentation to study site.

9.2 Data Submission Instructions

This study uses an Electronic Database Capture system for data submission through the data management services of HonorHealth. The original reports, traces and films must be retained by the Investigators for future reference.

Screening Form: at time of screening

Enrollment Form: after eligibility confirmed.

All screening/baseline/treatment/off-treatment Forms: within 2 weeks of occurrence.

Adverse Event Form: within 2 weeks of each scheduled adverse events evaluation until adverse events have resolved following permanent discontinuation of treatment, documenting adverse event information, including toxicities indicated by lab testing.

NOTE: all Serious Adverse Events must also be reported on the Adverse Event Form.

Serious Adverse Events (SAE) documentation: **submit directly to HonorHealth and the Site Principal Investigator** within the time frame and per the guidelines specified in Section 7.7. Any deaths that the site is notified of will be reported using the Adverse Event Form and submitted within 2 weeks of knowledge of death.

10 TERMINATION OF STUDY

HonorHealth reserves the right to discontinue this study at any time.

11 INVESTIGATOR'S PROTOCOL AGREEMENT

The Investigator must sign the Investigator's Protocol Agreement (Page 3 of this document). The original must be kept on file at HonorHealth and the Investigator must retain a copy. The completed Investigator's Protocol Agreement signifies agreement to comply with all procedures outlined by this protocol by the Investigator. An Investigator's Protocol Agreement must be signed if and when a protocol amendment is issued by HonorHealth.

12 REFERENCES

Assaf E, Verlinde-Carvalho M, Delbaldo C, Grenier J, Sellam Z, Pouessel D, Bouaita L, Baumgaertner I, Sobhani I, Tayar C, Paul M, Culine S. 5-Fluorouracil/Leucovorin Combined with Irinotecan and Oxaliplatin (FOLFIRINOX) as Second-Line Chemotherapy in Patients with Metastatic Pancreatic Adenocarcinoma. Oncology 2011;80:301-306 (DOI: 10.1159/000329803)

Alvarez, R, Musteanu M, Garcia-Garcia E, Lopez-Casas PP, Megias D, Guerra C, Munoz, M, Quijano Y, Cubillo A, Rodriguez-Pascual J et al. (2013) Stromal disrupting effects of nab-paclitaxel in pancreatic cancer. Br J Cancel 109, 926-933.

Atkinson, T.M., Mendoza, T.R., Sit, L., Passik, S., Scher, H.I., Cleeland, C.S., & Basch, E. (2010), *Pain Medicine 11*, 337-346.

Bellasi A, Galassi A, Salvi P, Cozzolino M. Paricalcitol and cardiorenal outcome: from the MPACT study to clinical practice. Blood Purif 2013: 36: 12-16. Dei: 10.1159/00350579.

Borazanci E, Jameson GS, Borad M, Ramanathan RK, Korn RL, Caldwell L, Ansaldo K, Hendrickson K, Marceau K, Von Hoff DD. A phase II pilot trial of nivolumab (N) + albumin bound paclitaxel (AP) + paricalcitol (P) + cisplatin (C) + gemcitabine (G) (NAPPCG) in patients with previously untreated metastatic pancreatic ductal adenocarcinoma (PDAC). J Clin Oncol 36, 2018 (suppl 4S; abstr 358)

Burris HA 3rd, Moore MJ, Andersen J, Green MR, Rothenberg ML, Modiano MR, Cripps MC, Portenoy RK, Storniolo AM, Tarassoff P, Nelson R, Dorr FA, Stephens CD, Von Hoff DD. Improvements in survival and clinical benefit with gemcitabine as first-line therapy for patients with advanced pancreas cancer: a randomized Trial. J Clin Oncol. 1997 Jun; 15(6):2403-13.

Chaput N, Lepage P, Coutzac C, Soularue E, Le Roux K, Monot C, Boselli L, Routier E, Cassard L, Collins M, Vaysse T, Marthey L, Eggermont A, Asvatourian V, Lanoy E, Mateus C, Robert C, Carbonnel F. Baseline gut microbiota predicts clinical response and colitis in metastatic melanoma patients treated with ipilimumab. Ann Oncol. 2017 Jun 1;28(6):1368-1379.

Cleeland CS, Mendoza TR, Wang XS, Chou C, Harle M, Morrissey M, & Engstrom MC. Assessing Symptom Distress in Cancer: The M. D. Anderson Symptom Inventory. Cancer 2000; 89:1634-1646.

Conroy T, Desseigne F, Ychou M, Bouché O, Guimbaud R, Bécouarn Y, Adenis A, Raoul J-L, Gourgou-Bourgade S, de la Fouchardière C, Bennouna J, Bachet J-B, Khemissa-Akouz F, Péré-Vergé D, Delbaldo C, Assenat E, Chauffert B, Michel P, Montoto-Grillot C, Ducreux M. FOLFIRINOX versus gemcitabine for metastatic pancreatic cancer. N Engl J Med. 2011;364:1817-1825

Cozzolino M., Brancaccio D, Cannella G, et al. VDRA therapy is associated with improved survival in dialysis patients with serum intact PTH ≥ 150 pg/ml: results of the Italian FARO study. Nephrol Dial. Transplant 2012;27:3588.94

Eisenhauer EA, Therasse P, Bogaerts J, Schwartz LH, Sargent D, Ford R, Dancey J, Arbuck S, Gwyther S, Mooney M, Rubinstein L, Shankar L, Dodd L, Kaplan R, Lacombe D, Verweij J. New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). Eur J Cancer. 2009 Jan; 45(2):228-47.

Frankel AE, Coughlin LA, Kim J, Froehlich TW, Xie Y, Frenkel EP, Koh AY. Metagenomic Shotgun Sequencing and Unbiased Metabolomic Profiling Identify Specific Human Gut Microbiota and Metabolites Associated with Immune Checkpoint Therapy Efficacy in Melanoma Patients. Neoplasia. 2017 Oct;19(10):848-855.

Evers L, Perez-Mancera PA, Lenkiewicz E, Tang N, Aust D, Knosele T, Rummele P, Holley T, Kassner M, Aziz M, Ramanathan R, Yin H, Von Hoff DD, Pilarsky C, Barrett M. STAG2 is a clinical relevant tumor suppressor in pancreatic ductal adenocarcinoma Genomic Med 2014; 6 (1) 9.

Frasci G, Panza N, Comella P, Nicolella GP, Natale M, Manzione L, Bilancia D, Cioffi R, Maiorino L, De Cataldis G, Belli M, Micillo E, Mascia V, Massidda B, Lorusso V, De Lena M, Carpagnano F, Contu A, Pusceddu G, Comella G. Cispatin, gemcitabine, and paclitaxel in locally advanced or metastatic non-small-cell lung cancer: A phase I-II study. J Clin Oncology. Journal of Clinical Oncology. 1999 Aug;17(8):2316-2325.

Frese KK, Neesse A, Cook N, Bapiro TE, Lolkema MP, Jodrell DI, Tuveson DA. Nab-paclitaxel potentiates gemcitabine activity by reducing cytidine deaminase levels in a mouse model of pancreatic cancer. Cancer Discovery. 2012;2(3):OF1-OF10. DOI: 10.1158/2159-8290.CD-11-0242

Gatalica, Z., Snyder, C., Maney, T., Ghazalpour, A., Holterman, D. A., Xiao, N., ... & Hamid, O. "Programmed Cell Death 1 (PD-1) and Its Ligand (PD-L1) in Common Cancers and Their Correlation with Molecular Cancer Type. Cancer epidemiology, biomarkers & prevention: a publication of the American Association for Cancer Research, cosponsored by the American Society of Preventive Oncology 23.12 (2014): 2965.

Goldstein D, El-Maraghi RH, Hammel P, Heinemann V, Kunzmann V, Sastre J, Scheithauer W, Siena S, Tabernero J, Teixeira L, Tortora G, Van Laethem JL, Young R, Penenberg DN, Lu B, Romano A, Von Hoff DD. Nab-Paclitaxel plus gemcitabine for metastatic pancreatic cancer: long-term survival from a phase III trial. J Natl Cancer Inst. 2015 Jan 31;107(2).

Gopalakrishnan V, Spencer CN, Nezi L, Reuben A, Andrews MC, Karpinets TV, Prieto PA, Vicente D, Hoffman K, Wei SC, Cogdill AP, Zhao L, Hudgens CW, Hutchinson DS, Manzo T, Petaccia de Macedo M, Cotechini T, Kumar T, Chen WS, Reddy SM, Szczepaniak Sloane R, Galloway-Pena J, Jiang H, Chen PL, Shpall EJ, Rezvani K, Alousi AM, Chemaly RF, Shelburne S, Vence LM, Okhuysen PC, Jensen VB, Swennes AG, McAllister F, Marcelo Riquelme Sanchez E, Zhang Y, Le Chatelier E, Zitvogel L, Pons N, Austin-Breneman JL, Haydu LE, Burton EM, Gardner JM, Sirmans E, Hu J, Lazar AJ, Tsujikawa T, Diab A, Tawbi H, Glitza IC, Hwu WJ, Patel SP, Woodman SE, Amaria RN, Davies MA, Gershenwald JE, Hwu P, Lee JE, Zhang J, Coussens LM, Cooper ZA, Futreal PA, Daniel CR, Ajami NJ, Petrosino JF, Tetzlaff

MT, Sharma P, Allison JP, Jenq RR, Wargo JA. Gut microbiome modulates response to anti-PD-1 immunotherapy in melanoma patients. Science. 2018 Jan 5 ; 359(6371):97-103.

Izquierdo MJ, Cavia M, Muniz P, et al. Paricalcitol reduces oxidative stress and inflammation in hemodialysis patients. BMC nephrology 2012; 13: 159.

Janjan NA, Wang XS, Mendoza TR, Zhang Y, Das P, Crane C, Delclos M, Krishnan S, Cleeland CS. Utility of the M. D. Anderson Symptom Inventory (MDASI) for symptom evaluation during chemoradiation in patients with gastrointestinal malignancies [abstract]. American Society of Clinical Oncology 43rd Annual Meeting, Chicago IL, Jun 1-5, 2007. J Clin Oncol 25(18 Suppl), 2007; 6613.

Jameson Gayle, Borazanci E, Poplin E, Barrett M, Crowley J, et al. High Complete and partial response rate in a phase Ib/II trial with albumin-bound paclitaxel and gemcitabine plus cisplatin in patients with advanced pancreatic cancer. Poster presentation for AACR 2015 Annual Meeting, Philadelphia, PA. 18-22 APR 2015, Abstract LB-003.

Kaplan EL, Meier P. Nonparametric estimation from incomplete observations. J Am Stat Assoc. 1958;53:457-481.

Ketteler M, Martin KJ, Wolf M, Amdahl M, Cozzolino M, Goldsmith D, Sharma A, Marx S, Khan S. Paricalcitol versus cinacalcet plus low-dose Vitamin D therapy for the treatment of secondary hyperparathyroidism in patients receiving hemodialysis: results of the IMPACT SHPT study. Nephrol Dial. Transplant. 2012 Aug:27(8):3270-8.

Lawrence JA, Akman SA, Melin SA, Caswe LD, Schwartz GG. Oral paricalcitol (19 nor-1α, 25-dihydroxyvitamin D2) in women receiving chemotherapy for metastatic breast cancer: A feasibility trial. Cancer Biol Ther 14:476-80, 2013.

Le, DT, Lutz E, Uram JN, Sugar EA, Onners B, Sollt S, Zheng L, Diaz LA, Jr., Donehower RC, Jaffee EM et al. (2013) Evaluation of ipilumumab in combination with allogenic pancreatic tumor cells transfected with a GM-CSF gene in previously treated pancreatic cancer. J Immunother 36, 382-389.

Liang WS, Craig DW, Carpten J, Borad MJ, Demeure MJ, Weiss GJ, Izatt T, Sinari S, Christoforides A, Aldrich J, Kurdoglu A, Barrett M, Phillips L, Benson H, Tembe W, Braggio E, Kiefer JA, Legendre C, Posner R1, Hostetter GH, Baker A, Egan JB, Han H, Lake D, Stites EC, Ramanathan RK, Fonseca R, Stewart AK, Von Hoff DD. Genome-wide characterization of pancreatic adenocarcinoma patients using massively parallel sequencing. PLos ONE. 2012 Oct 10;7(10):e43192. doi:10.1371/journal.pone.0043192.

Meadors N, Floyd J, Perry MC. Pulmonary toxicity of chemotherapy. Semin Oncol. 2006;33(1):98-105.

Noerterheuser PA, Pradhan RS, Klein CE, Williams LA, Palaparthy R, Garimella TS, Lichtenberger O, Awni WM. Exposure-clinical response analysis of paricalcitol in patients with chronic kidney disease (Stage 5) on hemodialysis or peritoneal dialysis. J Clin Pharmacol. 2012 Aug;52 (8):1162-73.

Nomi T[1], Sho M, Akahori T, Hamada K, Kubo A, Kanehiro H, Nakamura S, Enomoto K, Yagita H, Azuma M, Nakajima Y. Clinical significance and therapeutic potential of

the programmed death-1 ligand/programmed death-1 pathway in human pancreatic cancer. Clin Cancer Res. 2007 Apr 1;13(7):2151-7.

Peddi PF, Want J, Gaos F, Wang-Gilliam A, Cho M., Nab-paclitaxel monotherapy in refractory pancreatic adenocarcinoma J Gastrointest Oncol. 2013 Dec; 4(4): 370–373. doi: 10.3978/j.issn.2078-6891.2013.034

Rahib L, Smith BD, Arzenberg R, Rsenzweig AB, Fleshman JM, Matrisian LM. (2014) Projecting cancer incidence and deaths to 2030: the unexpected burden of thyroid, liver, and pancreas cancers in the United States. Cancer Res. 74, 2913-2921

Reni M, Cereda S, Mazza E, Passoni P, Nicoletti R, Balzano G, Zerbi A, Arcidiacono PG, Staudacher C, Di Carlo V. PEGF (cisplatin, epirubicin, 5-fluorouracil, gemcitabine) regimen as second-line therapy in patients with progressive or recurrent pancreatic cancer after gemcitabine-containing chemotherapy. Am J Clin Oncol. 2008;31:145-150.

Rowinsky EK, Donehower RC. Paclitaxel (taxol). N. Engl J Med. 1995;332(15):1004-14.

Royal RE, Levy C, Turner K, Mathur A, Hughes, M, Kammula US, Sherry RM, Topalian SL, Yang J, Lowy, I, (2020). Phase II trial of single agent ipilumumab (anti-CTLA-4) for locally advanced or metastatic pancreatic adenocarcinoma. J Immunother 33, 828-833

Schwartz GG, Hall MC, Stindt D, Patton S, Lovato J, Totri FM. Phase I/II study of 19-nor-1α, 25-dihydroxyvitamin D2 (paricalcitol) in advanced androgen-insensitive prostate cancer. Clin Cancer Res 11:8680-5, 2005.

Sherman MH, Yu R, Engle DD, Ding N, Atkins AR, Tiriac H, Collisson EA, Connor F, Van Dyke T, Kozlov S, et al. (2014) Vitamin D receptor-mediated stromal reprogramming suppresses pancreatitis and enhances pancreatic cancer therapy. Cell 159, 80-93.

Siegal RL, Miller KD, Jemal A. (2015). Cancer Statistics, 2015. CA Cancer J Clin 65, 5-29.

Tonbul HZ, Solak Y, Atalay H, Turkmen K, Altintepe L. Efficacy and tolerability of intravenous paricalcitol in calcitriol-resistant hemodialysis patients with secondary hyperparathyroidism: 12-month prospective study. Ren Fall. 2012;34(3)297-303.

Torre LA, Bray F, Siegel RL, Ferlay J, Lortet-Tieulent J, Jemal A. (2015) Global cancer statistics. 2012 CA Cancer J CLin 65, 87-108.

Von Hoff DD, Ervin T, Arena FP, Chiorean EG, Infante J, Moore M, Seay T, Tjulandin SA, Ma WW, Saleh MN, Harris M, Reni M, Dowden S, Laheru D, Bahary N, Ramanathan RK, Tabernero J, Hidalgo M, Goldstein D, Van Cutsem E, Wei X, Iglesias J, Renschler MF. Increased survival in pancreatic cancer with nab-paclitaxel plus Gemcitabine. N ENGL J MED. 2013 OCT 31;369(18):1691-703. DOI: 10.1056/NEJMOA1304369. EPUB 2013 OCT 16.

Von Hoff DD, Ramanathan RK, Borad MJ, Laheru DA, Smith LS, Korn RL, Trieu V, Iglesias JL, Zhang H, Soon-Shiong P, Shi T, Rajeshkumar NV, Maiitra A, Hidalgo M. Gemcitabine plus nab-paclitaxel is an active regimen in patients with advanced pancreatic cancer: a phase I/II Trial. J Clin Oncol. 2011;29;4548-4554.

Von Hoff DD, Ramanathan RK, Evans DB, Demeure MJ, Maney T, Wright B, Gatalica Z, McGinniss MJ. Actionable targets in pancreatic cancer detected by immunohistochemistry (IHC), microarray (MA) fluorescent in situ hybridization (FISH), and mutational analysis. J Clin Oncology. 2012;30s: abstr 4013.

Wang XS, Williams LA, Eng C, Mendoza TR, Shah NA, Kirkendoll KJ, Shah PK, Trask PC, Palos GR, Cleeland CS. Validation and application of a module of the M. D. Anderson Symptom Inventory for measuring multiple symptoms in patients with gastrointestinal cancer (the MDASI-GI). *Cancer* 116(8): 2053-2063, 2010.

Williams, L.A., Gonzalez, G., Ault, P., Mendoza, T.R., Sailors, M.L., Williams, J.L. , Huang, F, Nazha, A., Kantarjan, H.M., Cleeland, C.S., & Cortes, J.E. (2013). *Blood, 122*(5), 641-647.

13 APPENDICES

APPENDIX A: SCHEDULE OF EVALUATIONS AND TREATMENT

Assessment	Screening within 21 days	Cycle 1 – 4+																After cycle each cycle (+/- 2 days)	At time of CR by CT scan and marker	EOS/ Early Term[10]	Survival FU
		Day 1	Day 2*	Day 4*	Day 8*	Day 9*	Day 12*	Day 15*	Day 18*	Day 22*	Day 23*	Day 26*	Day 29*	Day 30*	Day 32*	Day 36*	Day 39*				
Signed Informed Consent	x																				
Review Inclusion/ Exclusion	x	x																			
Medical History[1]	x	x			x			x		x			x								
Physical Examination	x	x			x			x		x			x							x	
Height (cm)	x																				
Weight (kg)	x	x			x			x		x			x							x	
BSA Calculation		x								x[2]											
Vital Signs	x	x			x			x		x			x							x	
Karnofsky PS	x	x			x			x		x			x							x	
CT/MRI scan/ tumor measurements[3]	x																	x			
PET/CT[4]																			x		
ECG	x																				
CBC with differential with Plts	x	x			x			x		x			x			x				x	

Assessment	**Screening within 21 days**	**Cycle 1 – 4+**																**After cycle each cycle (+/- 2 days)**	**At time of CR by CT scan and marker**	**EOS/ Early Term[10]**	**Survival FU**
		Day 1	**Day 2***	**Day 4***	**Day 8***	**Day 9***	**Day 12***	**Day 15***	**Day 18***	**Day 22***	**Day 23***	**Day 26***	**Day 29***	**Day 30***	**Day 32***	**Day 36***	**Day 39***				
Serum Chemistries[5]	x	x			x			x		x			x			x				x	
CA 19-9 (or CA125,or CEA if not expressors of CA19-9)	x	x								x										x	
Urinalysis[6]	x	x								x										x	
TSH[15]	x	x								x										x	
Blood Sample for Exploratory Biomarkers		x																			
Fecal Sample Collection	x[19]																x[20]				
Vitamin D Levels serum	x																				
Coagulation Panel[16]	x																				
Archived blocks of tumor specimen for CGH and Immune Assays[7]	x																				
Serum pregnancy[17]	x	x								x										x	
Con Meds[8]	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x			x	
Adverse Events[9]		x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x			x	
Telephone Follow up																					x
Nivolumab[13]		x						x					x								

Assessment	**Screening within 21 days**	**Cycle 1 – 4+**																**After cycle each cycle (+/- 2 days)**	**At time of CR by CT scan and marker**	**EOS/ Early Term[10]**	**Survival FU**
		Day 1	**Day 2***	**Day 4***	**Day 8***	**Day 9***	**Day 12***	**Day 15***	**Day 18***	**Day 22***	**Day 23***	**Day 26***	**Day 29***	**Day 30***	**Day 32***	**Day 36***	**Day 39***				
Albumin-bound Paclitaxel[12]		x			x					x			x								
Cisplatin[12]		x			x					x			x								
Gemcitabine[12]		x			x					x			x								
Paricalcitol[14]		x[14]		x[14]	x[14]		x[14]	x[14]	x[14]	x[14]		x[14]	x[14]		x[14]	x[14]	x[14]				
Neulasta						x								x							
Optional IV fluids			x			x					x			x							
MDASI-GI and BPI Questionnaires [18]	x	x			x			x		x			x			x				x	
* Visit windows will be +/- 24 hours as indicated. All assessments that occur on dosing days mush occur within 24 hours prior to dosing.																					

Schedule of Events footnotes:

1. To include concurrent baseline conditions (using NCI CTCAE, version 4.0), prior cancer therapy (including documentation of prior surgery, adjuvant or neoadjuvant chemotherapy and radiotherapy).
2. BSA is recalculated on Day 1 of each cycle. Drug doses will be recalculated only if there has been a ≥10% change in body weight from baseline. (See Section 4.3).
3. Computed tomography (CT) / magnetic resonance imaging (MRI) scan to document disease status (including chest, abdomen, pelvis, and other regions as clinically indicated. In addition, brain scan required to exclude brain metastases). If a CT scan was taken within 28 days prior to first dose, a new scan is not necessary. However, if a new scan is to be done, it should be performed as close to start of chemotherapy as possible. . In addition to the CT / MRI scan, tumor size may also be assessed utilizing visual or palpable lesions on physical examination including full assessment of all known metastases (see RECIST 1.1 criteria in Section 7). Follow-up scans are due every 6 weeks, (prior to each cycle)
4. When a CR is documented, a confirmatory PET scan will be obtained.
5. To include BUN, phosphorus, magnesium, creatinine, total protein, albumin, calcium, glucose, total bilirubin, alkaline phosphatase, AST, ALT, and electrolytes (chloride, sodium, potassium, and bicarbonate) and CA 19-9 (or CA 125, or CEA if not expressers of CA 19-9).
6. Lab urinalysis with micro, culture if indicated- to include protein, specific gravity, glucose, and blood.
7. Archived paraffin block of tumor specimen, if collected, prior to treatment.
8. To include all medications taken within 30 days prior to study enrollment.
9. Patient will be followed until resolution of any drug-related AE or SAE occurring during the study, including, within 30 days of last administration of study medication, or when the patient begins alternative therapy; whichever is sooner.
10. End of Study or Early Termination assessments can be completed 14-28 (+/- 2) days from the last dose of study medication
11. Follow-up assessments by telephone will be conducted in all patients every 12 weeks, start from last dose of chemotherapy, to determine date of response, date of disease progression, and date of death.
12. The sequence of drug administration is albumin-bound paclitaxel, then cisplatin, then gemcitabine.
13. Nivolumab is given every 2 weeks
14. Paricalcitol is given 2 times per week days 1,4,8,12,15,18,22,26,29,32,36,39 etc, (+/- 1 day allowed for dosing)
15. If TSH is abnormal, obtain T3 and free T4 levels
16. Coagulation Panel to include PTT and PT/INR
17. Performed only for women of child bearing potential
18. There will be a +/- 48 hour completion window for the MDASI-GI and BPI Questionnaires
19. At home collection kit shall be provided at screening to be collected and returned within 72 hours of C1D1 pre-dose.
20. At home collection kit shall be provided on C(X)D39 and is to be collected and returned within 72 hours of C(X)D1.

APPENDIX B: KARNOFSKY PERFORMANCE STATUS

Karnofsky Performance Status		
	Score	**Descriptions**
Able to carry on normal activity and to work; no special care needed.	100	Normal: no complaints; no evidence of disease
	90	Able to carry on normal activity; minor signs or symptoms of disease
	80	Normal activity with effort; some signs or symptoms of disease
Unable to work; able to live at home and care for most personal needs; varying amount of assistance needed.	70	Cares for self; unable to carry on normal activities or to do active work
	60	Requires occasional assistance, but is able to care for most of personal needs
	50	Requires considerable assistance and frequent medical care
Unable to care for self; requires equivalent of institutional or hospital care; disease may be progressing rapidly.	40	Disabled: requires special care and assistance
	30	Severely disabled: hospital admission is indicated although death not imminent
	20	Very sick: hospital admission necessary; active supportive treatment needed
	10	Moribund: fatal processes are progressing rapidly
	0	Dead

APPENDIX C: LIST OF ABBREVIATIONS

Term	Definition
Abraxis	Abraxis BioScience, Inc
ADR	Adverse Drug Reaction
AE	Adverse Event
ALT (SGPT)	Alanine Aminotransferase (SGPT)
ANC	Absolute Neutrophil Count
ASCO	American Society of Clinical Oncology
AST (SGOT)	Aspartate Aminotransferase (SGOT)
AUC	Area Under the Curve
BCC	Basal Cell Carcinoma
β-hCG	Beta subunit of human chorionic gonadotrophin (hCG)
BMS	Bristol-Myers Squibb
BSA	Body Surface Area
BUN	Blood Urea Nitrogen
˚C	Degrees Celsius
CA 125	Carbohydrate Antigen 125
CA19-9	Carbohydrate Antigen 19-9
CBC	Complete Blood Count
CEA	Carcinoembryonic antigen
CFR	Code of Federal Regulations
CGH	Comparative Genomic Hybridization
CI	Confidence Interval
CIB	Clinical Investigator's Brochure
C_{max}	Maximum observed plasma concentration
CMH	Cochran-Mantel-Haenszel
CML	Chronic myelogenous leukemia
CrEL	Cremophor-EL
CRF	Case Report Form
CR	Complete Response

Term	Definition
CRO	Contract Research Organization
CT	Computed Tomography
CTCAE	Common Terminology Criteria for Adverse Events
DHHS	Department of Health and Human Services
DLT	Dose Limiting Toxicity
DSMC	Data Safety and Monitoring Committee
DVT	Deep Vein Thrombosis
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
EPR	Enhanced Permeability and Retention
EORTC	European Organization for Research and Treatment of Cancer
EORTC QLQ-C30	Questionnaire to assess quality of life of patients with cancer
EORTC QLQ-BM22	EORTC QLQ Bone metastases module
EOS	End of Study
FAS	Full Analysis Set
˚F	Degrees Fahrenheit
FDA	United States Food and Drug Administration
GCP	Good Clinical Practice(s)
G-CSF	Granulocyte Colony-Stimulating Factor
GFR	Glomerular Filtration Rate
GTX	Gemzar® plus Taxotere® plus Xeloda®
HA	Human Albumin
HBsAg	Hepatitis B surface antigen
HCV	Hepatitis C antibody
Hgb	Hemoglobin
Hh	Hedgehog
HIV	Human Immunodeficiency Virus
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee

Term	Definition
IND	Investigational New Drug
INR	International Normalized Ratio
IRB	Institutional Review Board
IV	Intravenous(ly)
KPS	Karnofsky Performance Status
LDH	Lactate Dehydrogenase
MedDRA	Medical Dictionary for Regulatory Activities
MR	Minor Response
MRI	Magnetic Resonance Imaging
MTD	Maximum Tolerated Dose
NCI	National Cancer Institute
NCI-CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
ND	Not Done
NIH	National Institutes of Health
non-DEHP	Non-(di(2-ethylhexyl) phthalate)
ORR	Overall Response Rate
PD	Progressive Disease
PDAC	Pancreatic Ductal Adenocarcinoma
PET	Positron-Emission Tomography
PFS	Progression Free Survival
P-gp	P-glycoprotein
PK	Pharmacokinetics
PPS	Per Protocol Set
PR	Partial Response
PT	Prothrombin Time
PTT	Partial Thromboplastin Time
QD	Daily
RECIST	Response Evaluation Criteria in Solid Tumors
SAE	Serious Adverse Event

Term	Definition
SAF	Safety Analysis Set
SAP	Statistical Analysis Plan
SCLC	Small-cell lung cancer
SD	Stable Disease
S.D.	Standard Deviation
SGOT	Serum Glutamate Oxaloacetic Transaminase
SGPT	Serum Glutamate Pyruvic Transaminase
SOP	Standard Operating Procedure
SPARC	Secreted Protein Acidic and Rich in Cysteine (a glycoprotein)
SUV	Standard Uptake Value
T_{max}	Time of Maximum Observed Plasma Concentration
TEAE	Treatment Emergent Adverse Event
TEAV	Treatment Emergent Abnormal Laboratory Value
TGen	Translational Genomics Research Institute
TKI	Tyrosine Kinase Inhibitor
TTP	Time to Progression
ULN	Upper Limit of Normal
US	United States
WBC	White Blood Cell
WCBP	Women of Child-Bearing Potential
WHO	World Health Organization
WHODD	WHO Drug Dictionary

APPENDIX D: REVISED NATIONAL CANCER INSTITUTE COMMON TERMINOLOGY CRITERIA FOR ADVERSE EVENTS (NCI CTCAE), VERSION 4.0 (PUBLISHED 28 MAY 2009)

Revised National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE), version 4.0 (published 28 May 2009)

The National Cancer Institute (NCI) Cancer Therapy Evaluation Program (CTEP) Common Terminology Criteria for Adverse Events (CTCAE), version 4.0 can be viewed on-line at the following NCI web site:

http://evs..nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-06-14_QuickReference_8.5x11.pdf

APPENDIX E: STUDY DRUG PREPARATION, DOSING, ADMINISTRATION AND STORAGE

See links below to website access

Nivolumab (OPDIVO™) Prescribing Information (updated 2014) – Accessed via OPDIVO Website http://www.opdivo.bmscustomerconnect.com/gateway

Albumin-bound paclitaxel (Abraxane™) Prescribing Information (Updated 1/2012) – Accessed via Abraxane Website: http://www.abraxane.com/docs/Abraxane_PrescribingInformation.pdf

Cisplatin Prescribing Information (updated 2012) – Accessed via Daily Med (National Library of Medicine) http://dailymed.nlm.nih.gov/dailymed/lookup.cfm?setid=a440f077-46f6-4688-a209-65bce38d1c92

Gemcitabine (Gemzar™) Prescribing Information (Updated 2/2011) – Accessed via Gemzar Website: http://pi.lilly.com/us/gemzar.pdf

Paricalcitol (Zemplar®) Prescribing Information (Updated 2012) – Accessed via Zemplar Website http://www.zemplar.com/

APPENDIX F: 2006 UPDATE OF ASCO PRACTICE GUIDELINE RECOMMENDATIONS FOR THE USE OF WHITE BLOOD CELL GROWTH FACTORS: GUIDELINE SUMMARY

Setting/Indication	Recommendation
Primary prophylaxis	Primary prophylaxis is recommended for the prevention of FN in patients who have a high risk of FN based on age, medical history, disease characteristics, and myelotoxicity of the chemotherapy regimen. For “dose-dense” regimens, CSF is required and recommended. Clinical Trial data support the use of CSF when the risk of FN is in the range of 20% or higher.
Primary prophylaxis: Special circumstances	Certain clinical factors predispose to increased complications from prolonged neutropenia, including: patient age > 65 years; poor performance status; previous episodes of FN; extensive prior treatment including large radiation ports; administration of combined chemoradiotherapy; bone marrow involvement by tumor-producing cytopenias; poor nutritional status; the presence of open wounds or active infections; more advanced cancer, as well as other serious comorbidities. In such situations, primary prophylaxis with CSF is often appropriate, even with regimens with FN rates of < 20%.
Secondary prophylaxis	Secondary prophylaxis with CSF is recommended for patients who experienced a neutropenic complication from a prior cycle of chemotherapy (for which primary prophylaxis was not received), in which a reduced dose may compromise disease-free or overall survival or treatment outcome. In many clinical situations, dose reduction or delay may be a reasonable alternative.
Therapeutic use: Afebrile neutropenia	CSF should not be routinely used for patients with neutropenia who are afebrile.
Therapeutic use: Febrile neutropenia	CSF should not be routinely used as adjunctive treatment with antibiotic therapy for patients with fever and neutropenia. However, CSF should be considered in patients with fever and neutropenia who are at high-risk for infection-associated complications, or who have prognostic factors that are predictive of poor clinical outcomes. High-risk features include expected prolonged (> 10 days) and profound (< 0.1 × 109/L) neutropenia, age > 65 years, uncontrolled primary disease, pneumonia, hypotension and multi-organ dysfunction (sepsis syndrome), invasive fungal infection, or being hospitalized at the time of the development of fever.
Dose intensity/density of chemotherapy	Dose-dense regimens should only be used within an appropriately designed clinical Trial or if supported by convincing efficacy data.

Setting/Indication	Recommendation
Adjuncts to progenitor-cell transplantation	Administration of CSF to mobilize PBPC often in conjunction with chemotherapy, and their administration after autologous, but not allogeneic, PBPC transplantation is the current standard of care.
AML: Initial or repeat induction chemotherapy	CSF use following initial induction therapy is reasonable, though there has been no favorable impact on remission rate, remission duration, or survival. Patients > 55 years of age may be most likely to benefit from CSF use.
AML: CSF for priming effects	Use of CSF for priming effects is not recommended.
AML: Consolidation chemotherapy	CSF use can be recommended after the completion of consolidation chemotherapy because of the potential to decrease the incidence of infection and eliminate the likelihood of hospitalization in some patients receiving intensive postremission chemotherapy. There seems to be more profound shortening of the duration of neutropenia after consolidation chemotherapy for patients with AML in remission than for patients receiving initial induction therapy. As yet there is no information about the effect of longer-acting pegylated CSFs in patients with myeloid leukemias, and they should not be used in such patients outside of clinical Trials.
MDS	Intermittent administration of CSF may be considered in a subset of patients with severe neutropenia and recurrent infection.
ALL	CSF administration is recommended after the completion of the initial first few days of chemotherapy of the initial induction or first postremission course, thus shortening the duration of neutropenia of < 1,000/mm^3 by approximately 1 week.
Acute leukemia in relapse	CSF should be used judiciously, or not at all, in patients with refractory or relapsed myeloid leukemia since the expected benefit is only a few days of shortened neutropenia.
Radiotherapy ± chemotherapy	CSF should be avoided in patients receiving concomitant chemotherapy and radiation therapy, particularly involving the mediastinum. In the absence of chemotherapy, therapeutic use of CSF may be considered in patients receiving radiation therapy alone if prolonged delays secondary to neutropenia are expected.
Older patients	Prophylactic CSF for patients aged ≥ 65 years with lymphoma treated with curative chemotherapy (CHOP or more aggressive regimens) should be given to reduce the incidence of FN and infections.

Setting/Indication	Recommendation
Pediatric patients	As in adults, the use of G-CSF is reasonable for the primary prophylaxis of pediatric patients with a likelihood of FN. Similarly, the use of G-CSF for secondary prophylaxis or for therapy should be limited to high-risk patients. However, the potential risk for secondary myeloid leukemia or myelodysplastic syndrome associated with G-CSF represents a concern in children with ALL whose prognosis is otherwise excellent. For these reasons, the specific use of G-CSF in children with ALL should be considered carefully.
Comparative clinical activity of G-CSF and GM-CSF	No guideline recommendation can be made regarding the equivalency of the two colony-stimulating agents. Further Trials are recommended to study the comparative clinical activity, toxicity, and cost-effectiveness of GCSF and GM-CSF.
Treatment for radiation injury	Current recommendations for the management of patients exposed to lethal doses of total-body radiotherapy, but not doses high enough to lead to certain death due to injury to other organs, includes the prompt administration of CSF or pegylated G-CSF.

Abbreviations: CSF, colony-stimulating factors; FN, febrile neutropenia; PBPC, peripheral-blood progenitor cell; AML, acute myeloid leukemia; MDS, myelodysplastic syndrome; ALL, acute lymphocytic leukemia; CHOP, cyclophosphamide, doxorubicin, vincristine, prednisone; G-CSF, filgrastim; GM-CSF, sargramostim; pegylated G-CSF, pegfilgrastim.

APPENDIX G: MANAGEMENTALGORITHMS FOR ADVERSE EVENTS RELATED TO NIVOLUMAB THERAPY (FROM APPENDIX 3 OF INVESTIGATOR'S BROCHURE VERSION 13, 30 JUNE 2015 FROM BMS-936558/MDX 1106)

These general guidelines constitute guidance to the Investigator and may be supplemented by discussions with the Medical Monitor representing the Sponsor. The guidance applies to all immuno-oncology agents and regimens.

A general principle is that differential diagnoses should be diligently evaluated according to standard medical practice. Non-inflammatory etiologies should be considered and appropriately treated.

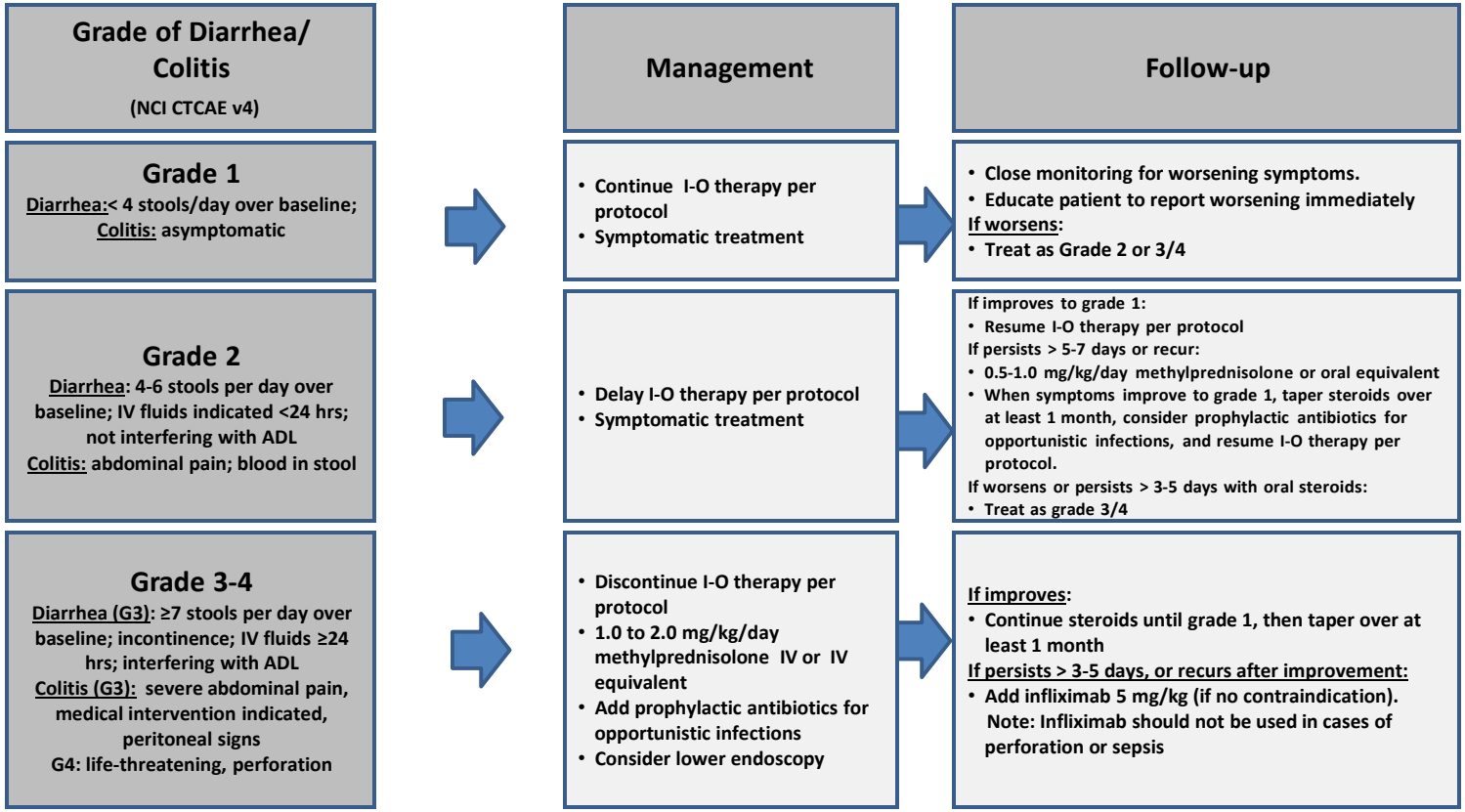
Corticosteroids are a primary therapy for immuno-oncology drug-related adverse events. The oral equivalent of the recommended IV doses may be considered for ambulatory patients with low-grade toxicity. The lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of oral corticosteroids.

Consultation with a medical or surgical specialist, especially prior to an invasive diagnostic or therapeutic procedure, is recommended.

The frequency and severity of the related adverse events covered by these algorithms will depend on the immuno-oncology agent or regimen being used.

GI Adverse Event Management Algorithm

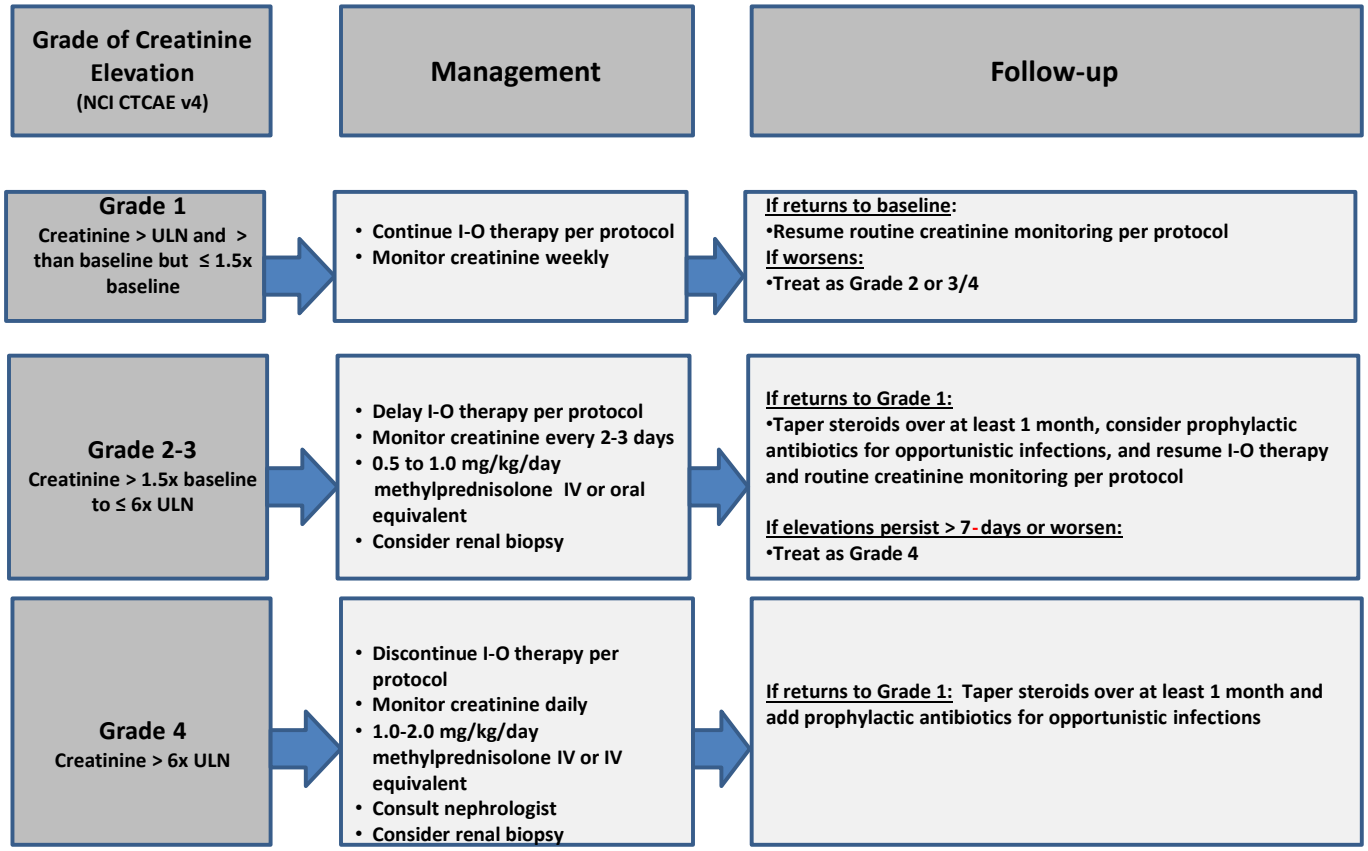
Rule out non-inflammatory causes. If non-inflammatory cause is identified, treat accordingly and continue I-O therapy. Opiates/narcotics may mask symptoms of perforation. Infliximab should not be used in cases of perforation or sepsis.



Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of oral corticosteroids.

Renal Adverse Event Management Algorithm

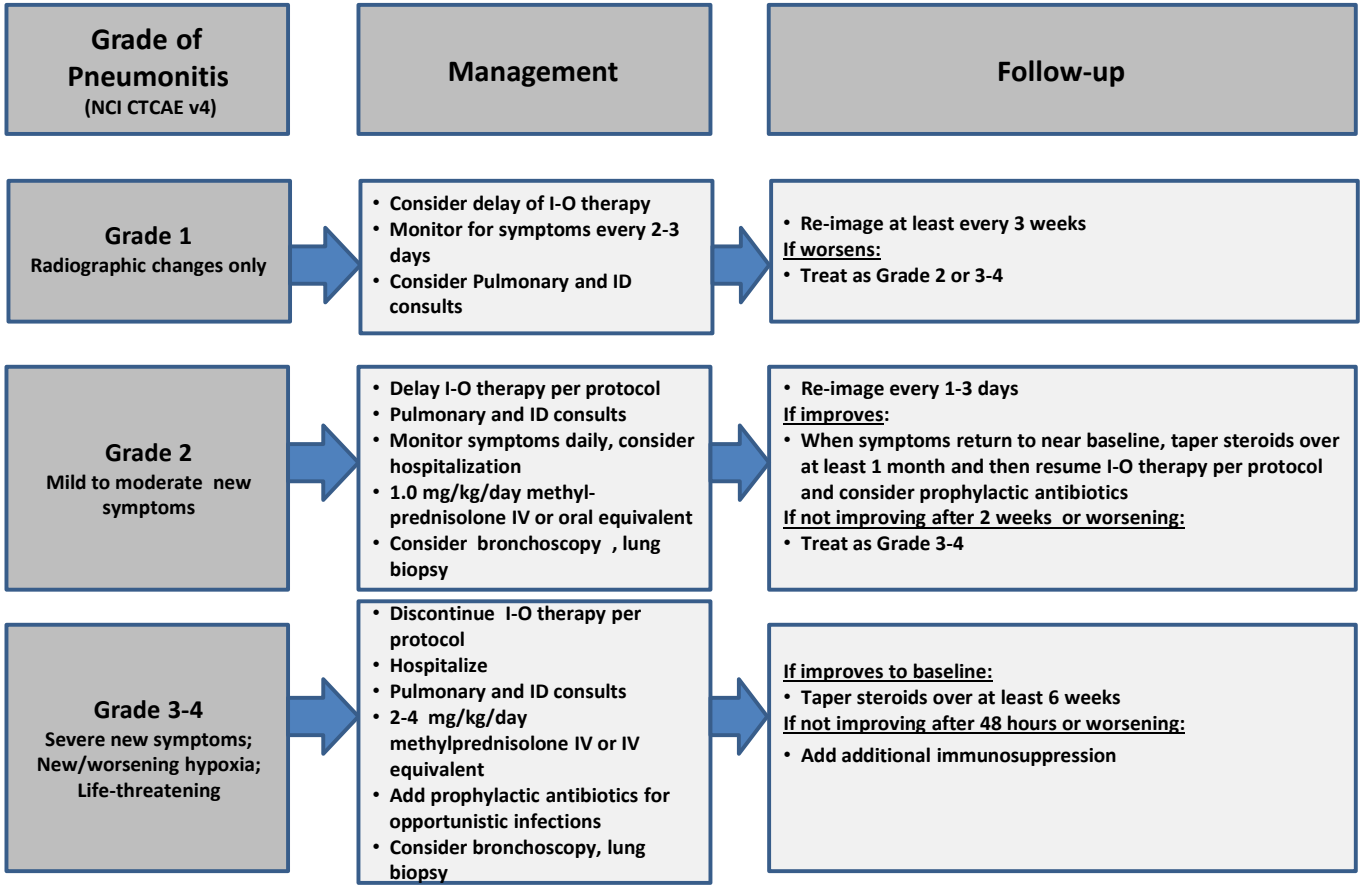
Rule out non-inflammatory causes. If non-inflammatory cause, treat accordingly and continue I-O therapy



Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of oral corticosteroids.

Pulmonary Adverse Event Management Algorithm

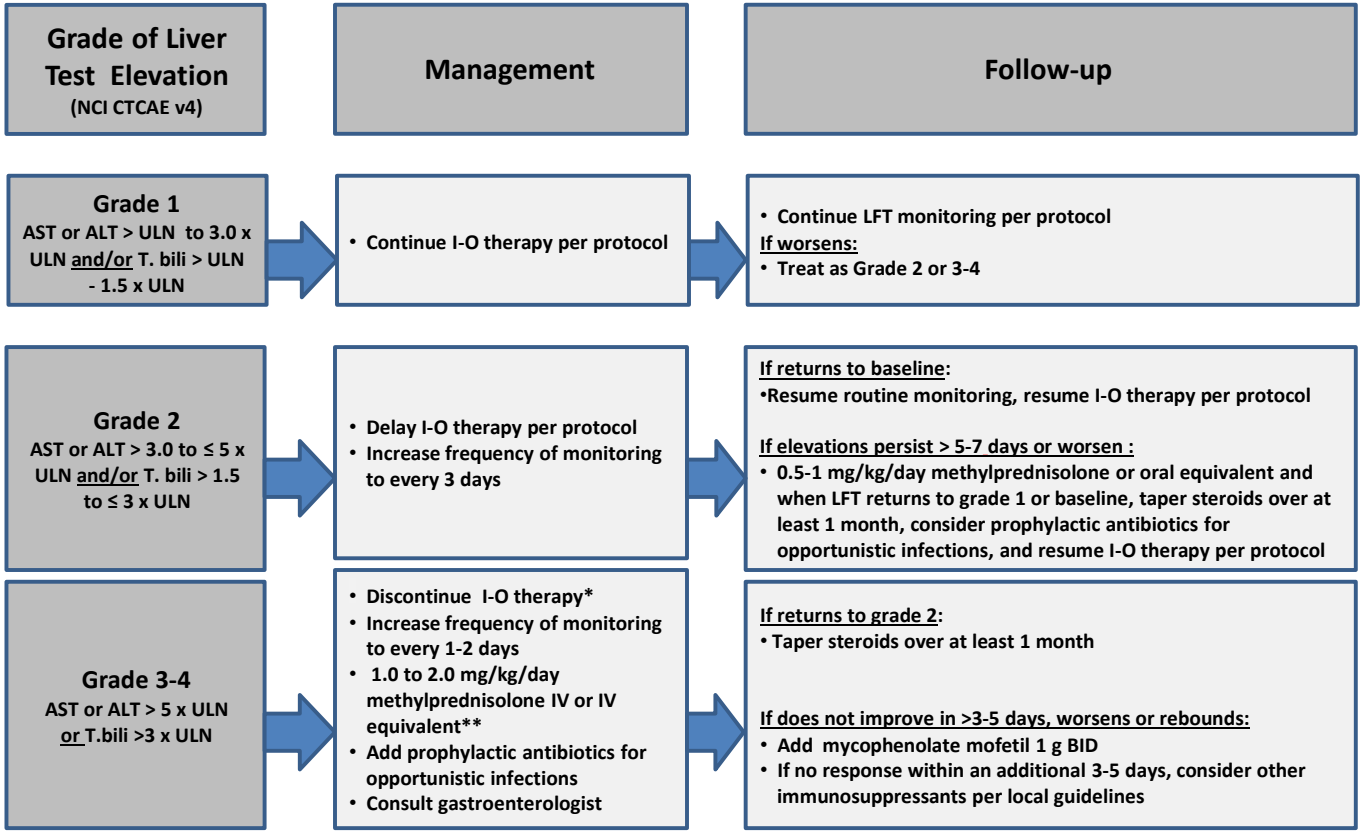
Rule out non-inflammatory causes. If non-inflammatory cause, treat accordingly and continue I-O therapy. Evaluate with imaging and pulmonary consultation.



Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of oral corticosteroids.

Hepatic Adverse Event Management Algorithm

Rule out non-inflammatory causes. If non-inflammatory cause, treat accordingly and continue I-O therapy. Consider imaging for obstruction.



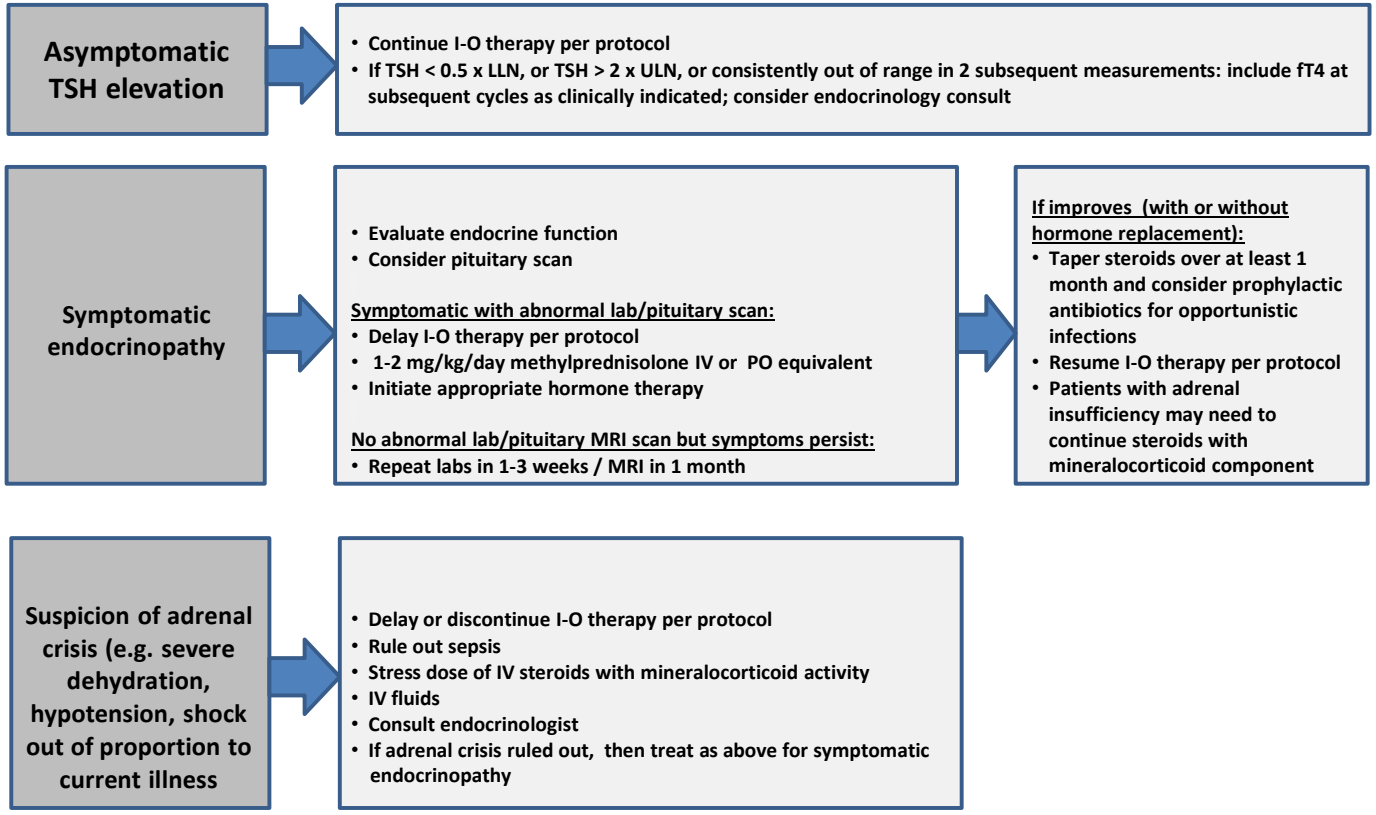
Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of oral corticosteroids.

***I-O therapy may be delayed rather than discontinued if AST/ALT ≤ 8 x ULN and T.bili ≤ 5 x ULN.**

**The recommended starting dose for grade 4 hepatitis is 2 mg/kg/day methylprednisolone IV.

Endocrinopathy Management Algorithm

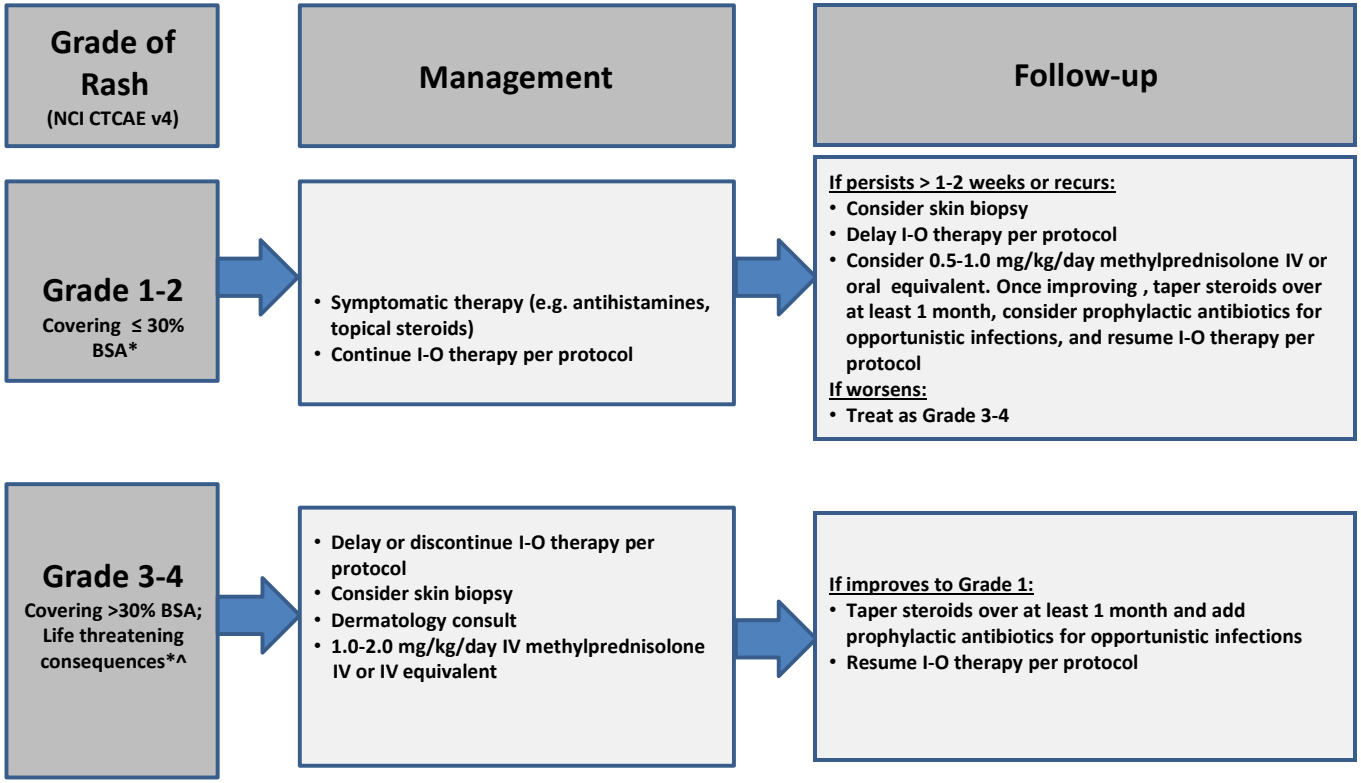
Rule out non-inflammatory causes. If non-inflammatory cause, treat accordingly and continue I-O therapy. Consider visual field testing, endocrinology consultation, and imaging.



Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of oral corticosteroids.

Skin Adverse Event Management Algorithm

Rule out non-inflammatory causes. If non-inflammatory cause, treat accordingly and continue I-O therapy.



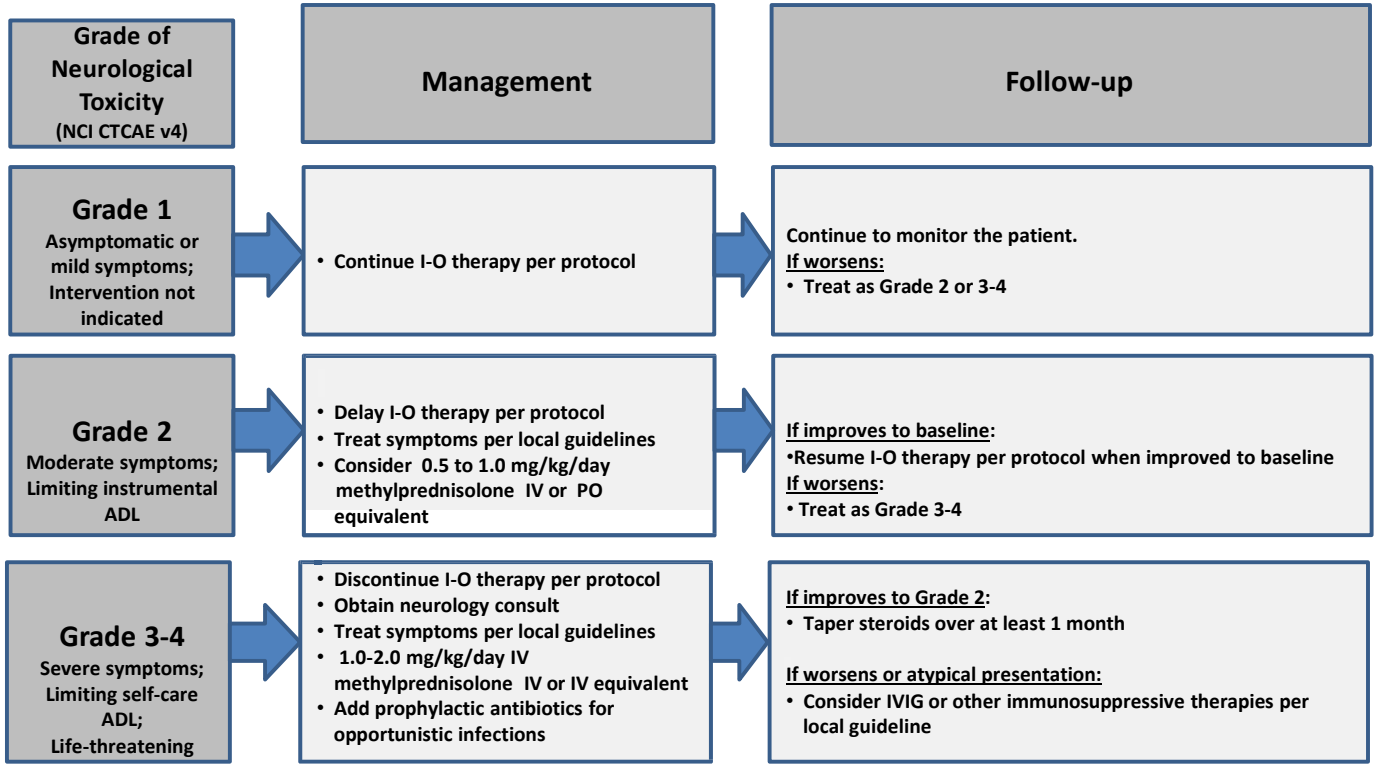
Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of oral corticosteroids.

*Refer to NCI CTCAE v4 for term-specific grading criteria.

^If SJS/TEN is suspected, withhold I-O therapy and refer patient for specialized care for assessment and treatment. If SJS or TEN is diagnosed, permanently discontinue I-O therapy.

Neurological Adverse Event Management Algorithm

Rule out non-inflammatory causes. If non-inflammatory cause, treat accordingly and continue I-O therapy.



Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of oral corticosteroids.

APPENDIX H: MEMO FOR DEXAMETHASONE DOSE REDUCTION WITH CONCOMITANT ADMINISTRATION OF FOSAPREPITANT

The current protocol recommends the following prophylactic medication regimen:

> *Aloxi (palonosetron) 0.25mg IV,* ***Emend (fosaprepitant) 150 mg IV and dexamethasone 20mg IV*** *within 30 minutes prior to treatment on days 1 and 8, repeated every 21 days. Patients will continue oral antiemetic prophylaxis at home with ondansetron 8mg bid and dexamethasone 4mg bid for 2 days after chemotherapy.*

Fosaprepitant is a moderate inhibitor of CYP3A4, resulting in an increased serum concentration of dexamethasone. The dose of dexamethasone, especially on day 1 and day 8, must be decreased to account for the drug-drug interaction.

Per EMEND® Prescribing Information for the 150mg (Single Dose Regimen of EMEND):

EMEND for Injection 150 mg is administered intravenously on Day 1 only as an infusion ***over 20-30 minutes*** *initiated approximately 30 minutes prior to chemotherapy. No capsules of EMEND are administered on Days 2 and 3. EMEND for Injection should be administered in conjunction with a corticosteroid and a 5-HT3 antagonist as specified in Table 1.*

Table 1
Recommended dosing (Single Dose Regimen of EMEND) for the prevention of nausea and vomiting associated with highly emetogenic cancer chemotherapy

	Day 1	Day 2	Day 3	Day 4
EMEND	150 mg intravenous	none	none	none
Dexamethasone*	12 mg orally	8 mg orally	**8 mg orally twice daily**	**8 mg orally twice daily**
5-HT_3 antagonist	See the package insert for the selected 5-HT_3 antagonist for appropriate Dosing information.	none	none	none

* Dexamethasone should be administered 30 minutes prior to chemotherapy treatment on Day 1 and in the morning on Days 2 through 4. **The dose of dexamethasone accounts for drug interactions.**

Due to similar bioavailability of oral and IV dexamethasone, the IV dexamethasone dose should be decreased to 12mg as recommended. The protocol has already conservatively adjusted the dose of oral dexamethasone on days 2 and 3 of treatment to 4mg BID. The next protocol amendment will reflect this recommendation.

Karen Ansaldo, PharmD, BCPS
Virginia G. Piper Cancer Center Clinical Trials
Scottsdale Healthcare
10510 N. 92nd St., Suite 200
Scottsdale, AZ 85258

APPENDIX I: THE MD ANDERSON SYMPTOM INVENTORY GASTROINTESTINAL CANCER MODULE (MDASI-GI) (TO BE SUBMITTED SEPARATELY FROM PROTOCOL FOR IRB APPROVAL)

MD Anderson Symptom Inventory (MDASI) modules augment the 19 core MDASI symptom and interference items with additional items identified as unique to a particular patient population. MDASI modules may be disease-specific, disease-site-specific, or treatment-specific.

The MDASI gastrointestinal cancer module (MDASI-GI) is a site-specific module. Along with the core MDASI's 13 symptom items and 6 interference items, the MDASI-GI also assesses 5 symptoms specific to gastrointestinal cancer:

- Constipation
- diarrhea or watery stools
- difficulty swallowing
- change in taste
- feeling bloated

MDASI-GI Features

- Purpose: To assess the severity of multiple gastrointestinal cancer-related symptoms and the impact of these symptoms on daily functioning
- Population: Patients with symptoms caused by gastrointestinal cancer and its treatment
- Assessment areas: Severity of multiple symptoms and the impact of symptoms on daily functioning during the last 24 hours
- Method: Self-report; paper-and-pencil form or tablet PC (self-administered or via interview), or telephone-based interactive voice response (IVR) system
- Time required: Five minutes
- Scoring: Please see the MDASI User's Guide
- Reliability: Cronbach alpha reliability ranges from 0.80 to 0.87

APPENDIX J: THE BRIEF PAIN INVENTORY (BPI) – SHORT FORM (TO BE SUBMITTED SEPARATELY FROM PROTOCOL FOR IRB APPROVAL)

The Brief Pain Inventory (BPI) is available in two formats: the BPI short form, which is used for clinical trials and is the version used for the foreign-language translations; and the BPI long form, which contains additional descriptive items that may be clinically useful (for example, items that expand the possible descriptors of pain, such as burning, tingling, etc.). For brevity's sake and for the patient's ease of use, however, we recommend the short form of the BPI.

In response to the US Food and Drug Administration (FDA) guidance for the pharmaceutical industry on the use of patient-reported outcome measures in medical product development to support labeling claims, we have prepared a BPI User's Guide to provide documentation of the BPI's development and psychometric properties. The information offered therein addresses the recommendations in the FDA guidance and establishes the BPI's adequacy as a measure to support medical product claims.

BPI Features

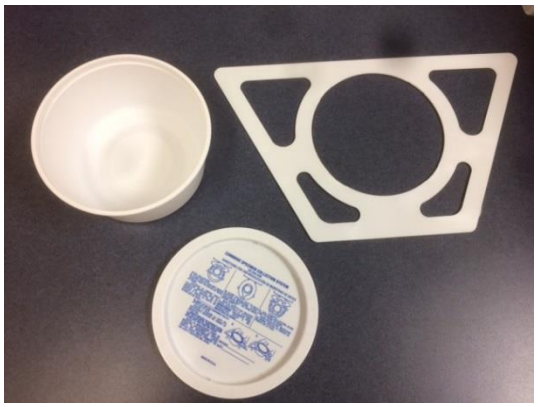
- Purpose: To assess the severity of pain and the impact of pain on daily functions
- Population: Patients with pain from chronic diseases or conditions such as cancer, osteoarthritis and low back pain, or with pain from acute conditions such as postoperative pain
- Assessment areas: Severity of pain, impact of pain on daily function, location of pain, pain medications and amount of pain relief in the past 24 hours or the past week
- Responsiveness: Responds to both behavioral and pharmacological pain interventions
- Method: Self-report or interview
- Time required: Five minutes (short form), 10 minutes (long form)
- Scoring: No scoring algorithm, but "worst pain" or the arithmetic mean of the four severity items can be used as measures of pain severity; the arithmetic mean of the seven interference items can be used as a measure of pain interference
- Reliability: Cronbach alpha reliability ranges from 0.77 to 0.91

APPENDIX K: FECAL SAMPLES FOR 16S GUT MICROBIOME/MYCOBIOME RRNA ANALYSIS [CHAPUT ET AL 2017]

The instructions below will be provided to each subject and will be submitted separately for review.

Fecal Sample Collection Instructions (to be included in collection kit)

You have been provided with a Commode Specimen Collection System. The collection system includes three items: a specimen container, container lid, and container frame pictured below. Please follow the instructions below.



1. Assemble the container and frame, as pictured below.

2. Place the frame and container under the toilet seat and pushed the container all the way to the rear of the commode.
3. Defecate into the container without allowing any urine into the container.
4. Carefully retrieve the container from the commode and remove the frame.
5. Place the lid on the container as pictured.

6. Write the date and time of collection under your assigned subject ID on the label affixed to the lid. Please do NOT write anything else on the lid or container.
7. Place the specimen container inside the provided specimen bag.
8. Store the specimen container in the provided specimen bag in a cool place, such as a refrigerator (at approximately 4 °C). Sample can be transported in the car without need for ice packs as long as the car is air-conditioned. If the car is not air-conditioned, please transport specimen on ice to keep cool.
9. Return the sample to the clinic within 72-hours of collection. This should correspond with your next scheduled study visit. IMPORTANT: If you cannot return the collected sample within 72 hours of collection, please contact the study team to make arrangements for return of the sample.