Phase II Trial of Paclitaxel Plus Gemcitabine and Cisplatin in Urothelial Cancer

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Cancer Centers

Phase II Trial of Paclitaxel Plus Gemcitabine and Cisplatin in Urothelial Cancer

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The study is to be conducted according to the protocol and in compliance with Good Clinical Practice (GCP) and other applicable regulatory requirements.

Signature:_____ Date:_____
Robert J. Amato, D.O.

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PROTOCOL

1.0 OBJECTIVES

1.1 To determine the efficacy of paclitaxel plus gemcitabine and cisplatin administered to patients with advanced local or metastatic urothelial cancer.

1.2. To determine the qualitative and quantitative toxicity and reversibility of toxicity of the combination of paclitaxel plus gemcitabine and cisplatin treatment in patients with advanced local or metastatic urothelial cancer.

2.0 BACKGROUND

Although bladder cancer is one of the ten most common cancers [1], treatment options are suboptimal for metastatic disease, with median survival under 1 year for untreated disease, despite its known chemosensitivity [2]. Remarkably, the clinical expression of urothelial cancer has much in common with small-cell carcinoma of the lung; front-line therapy for both diseases has historically been based on cisplatin, growth rates and response rates are high, the CNS is a common second echelon site of metastatic disease, and the cures of grossly metastatic disease are distinctly uncommon. Chemotherapy changes the expectation of median survival from about 4 months with no therapy to approximately 15 months with available chemotherapy. Unfortunately, there are still very few 5-year survivors, despite front-line response rates now in the range of 70%. Non- localized bladder cancer remains largely incurable and usually rapidly fatal.

Cisplatin-based combination chemotherapy regimens like M-VAC (methotrexate, vinblastine, adriamycin, and cisplatin) and CMV (cisplatin methotrexate, and vinblastine) remains a standard of therapy for patients with advanced carcinoma of the urothelium [3,4]. The overall response rate (complete plus partial) to these cisplatin-based combination regimens ranged from 50% to 70%, with complete responses seen in 15%-25% of cases [5-7]. Nonetheless, almost all responding patients ultimately relapsed within the first year, with a median survival of approximately 12-14 months [8].

M-VAC produced a modest, although significant, survival benefit compared in randomized trials with cisplatin as a single agent, CAP or CISCA (cyclophosphamide, adriamycin, and cisplatin) [9], or a carboplatin-based regimen [10]. Long-term follow-up of M-VAC–treated patients showed 12.5 months median survival and >6 years disease-free survival in 3.7% of patients [11]. The results with M-VAC did not improve with dose-intensification of this combination, and adverse toxicity reactions were both frequent and severe [12-14]. The dismal long-term outcome these regimens led to a search for new treatment approaches.

2.1 Gemcitabine in urothelial cancer

Gemcitabine (Gemzar; Eli-Lilly and Company, Indianapolis, IN) is a pyrimidine antimetabolite that has single-agent activity against urothelial cancer in previously treated patients, with an overall response rate of 27%-28% [15,16]. Two trials evaluating gemcitabine in previously untreated patients showed response rates of 24.3%-28% [17,18].

Gemcitabine is a nucleoside analog of deoxycytidine in which two fluorine atoms have been inserted into the deoxyribofuranosyl ring. Once inside the cell, gemcitabine is rapidly phosphorylated by deoxycytidine kinase, the rate-limiting enzyme for the formation of the active metabolites, gemcitabine diphosphate (dFdCDP) and gemcitabine triphosphate (dFdCTP). Gemcitabine diphosphate inhibits ribonucleotide reductase, which is responsible for producing the deoxynucleotides required for DNA synthesis and repair. The subsequent decrease in cellular deoxynucleotides (particularly dCTP) favors gemcitabine triphosphate in its competition with dCTP for incorporation into DNA. Reduction in cellular dCTP is an important self-potentiating mechanism resulting in increased gemcitabine nucleotide incorporation into DNA. Other self-potentiating mechanisms of gemcitabine include increased formation of active gemcitabine di-and triphosphates, and decreased elimination of gemcitabine nucleotides. After gemcitabine nucleotide is incorporated on the end of the elongating DNA strand, one more deoxynucleotide is added, and thereafter the DNA polymerases are unable to proceed. This action, termed, "masked chain termination," appears to lock the drug into DNA because proofreading exonucleases are unable to remove gemcitabine nucleotide from this penultimate position. Incorporation of gemcitabine triphosphate into DNA is strongly correlated with the inhibition of further DNA synthesis. Compared with ara-C, gemcitabine serves as a better transport substrate, is phosphorylated more efficiently, and is eliminated more slowly. These differences, together with self-potentiation, masked chain termination and the inhibition of ribonucleotide reductase, which are not seen with ara-C, may explain why gemcitabine is, and ara-C is not, active in solid tumors [19]. This unique combination of metabolic properties and mechanistic characteristics suggests that gemcitabine is likely to be synergistic with other agents in combination with either ribonucleotide reductase inhibitors to increase their incorporation into replicating DNA or with agents that induce DNA damage and evoke DNA repair processes.

Previous studies suggested that the dose rate should be considered that produces maximal nucleotide analogue formation, with increased intensity being achieved by prolonging the duration of infusion [20,21]. In a phase I trial at MD Anderson Cancer Center, dose intensification was based on studies of gemcitabine's cellular pharmacokinetics. The accumulation of gemcitabine triphosphate by mononuclear cells was saturated by dose rates of 10 mg/m^2/min [22].

2.2 Gemcitabine combined with cisplatin

The cytotoxicity of cisplatin is associated with the formation of bifunctional DNA inter- and intra-strand crosslinks [23]. An increased capacity to remove these crosslinks by nucleotide excision repair is thought to be a mechanism of resistance to cisplatin. Yang et al. demonstrated that the gemcitabine triphosphate inhibits the removal of cisplatin adducts from DNA nucleotide excision repair, resulting in synergistic cytotoxicity of gemcitabine and cisplatin [24].

The combination of gemcitabine and cisplatin was evaluated in bladder cancer in phase II studies using different schedules of administration. In those studies, gemcitabine was administered on days 1, 8, and 15 every 4 weeks and cisplatin once every 4 weeks either on day 1 or 2 or on days 1, 8, and 15 [25-27]. In total, 116 patients were treated with this combination, with an overall response rate ranging from 41% to 71% and with complete response rates ranging from 25% to 35%. The median survival time was consistently reported to be 13 months in two of the studies [25,27].

Because of the high response rates found in these phase II trials using the above- mentioned combinations, randomized phase III trials comparing M-VAC with cisplatin/gemcitabine. The International trial of cisplatin and gemcitabine vs. M-VAC in 405 patients was conducted between November 1996 and September 1998, for a median follow-up of 19 months, with 334 progressive disease status and 274 deaths observed [28,29]. Based on this trial, there was no indication that cisplatin/gemcitabine was inferior to M-VAC (HR = 1.05), but it was substantially less toxic. Based on these data, cisplatin and gemcitabine became the standard chemotherapeutic option for urothelial cancer. However, given that outcomes were not improved over the previous M-VAC standard, the need remains for more effective treatment regimens [30].

2.3. Addition of taxanes

Several reports have described the antitumor activity of taxanes in combination with cisplatin in bladder cancer. The combination of paclitaxel and gemcitabine was shown to have a promising activity profile in bladder carcinoma [31]. Paclitaxel (Taxol; Bristol-Myers Squibb, Princeton, NJ) is extracted from the bark of the Pacific yew, *Taxus brevifolia.* It promotes tubulin assembly into the microtubules and inhibits depolymerization to free tubulin, thus blocking cells in the M phase of the cell cycle [32-34]. In preclinical studies, paclitaxel demonstrated high antitumor activity against multiple murine transplantable tumors, as well as against human tumor xenografts [33,34]. There have been reports of paclitaxel showing improved efficacy in treatment of urothelial cancer [35-37]. In patients with advanced urothelial carcinoma who had not received prior radiotherapy or systemic chemotherapy, paclitaxel given at a dose of 250 mg/m^2 by 24 hours continuous infusion every 3 weeks resulted in a response rate of 42%, including complete responses in 27% of patients [37].

Paclitaxel given in combination with cisplatin was evaluated in several early studies [38-40] that included a total of 115 patients, with an overall response rate ranging from 50% to 72%. Studies with the other widely used taxane, docetaxel, in combination with cisplatin has a reported response rate of 60% in one study including 25 patients [41]. Median survival was 13 months in one of the cisplatin/paclitaxel studies [40], 10.6 in the other, and 13.6 months in the cisplatin/docetaxel study [41].

2.4. Paclitaxel plus cisplatin and gemcitabine

Because cisplatin, gemcitabine, and paclitaxel have differing mechanisms of action and somewhat difference toxicity profiles, European researchers studied this combination under the rationale that the combination would provide good disease control while being well tolerated by patients [2,42,43]. Initial results showed an overall response rate of 78% and a median survival of 15.6 months. The long-term, phase III trial found that after >4.5 years of follow-up, the regimen of all three drugs together resulted in an overall response rate of 56% and overall survival of 15.8 months, compared with 43.6% response and 12.7 months survival in patients who received only gemcitabine with cisplatin. Toxicity was similar for both arms, with the regimens being well tolerated [2]. However, doses have differed among all the studies of this regimen [44,45], from as little as 60 mg/m^2 [42] to as much as 200 mg/m^2 [44], with little rationale given for choice of dose.

2.5. Rationale

The rationale of the present study is to develop a combination based on the pharmacokinetics and mechanisms of action of the agents paclitaxel plus gemcitabine and cisplatin, which are all known active agents in urothelial tumors. Gemcitabine may be synergistic with DNA-damaging drugs such as paclitaxel and cisplatin because it can antagonize DNA repair. We will investigate the combination in this Phase II study.

3.0 PATIENT ELIGIBILITY

3.1. Inclusion Criteria

3.1.1. All patients must have histologic demonstration of metastatic or locally unresectable transitional cell carcinoma of the urothelium. Minor components (<50% overall) of variants such as glandular or squamous differentiation, or evolution to more aggressive phenotypes, such as sarcomatoid, or small cell changes are acceptable. However, when these atypical histologies are dominant, other treatment approaches may be more appropriate, and such patients are not eligible.

3.1.2. All patients must have measurable or evaluable disease. In general, liver and lung lesions should be at least 1 cm, and patients with node-only disease should have lesions of ≥1.5 cm in the largest dimension. Patients with disease confined to bone may be eligible if a measurable lytic defect is present. Patients with a 3-dimensional mass or pelvic sidewall fixation on bladder examination under anesthesia are considered to have measurable disease.

3.1.3. All patients must have adequate physiologic reserves as evidenced by:

- Life expectancy of at least 12 weeks.
- Eastern Cooperative Oncology Group (ECOG) performance status of ≤2.
- No clinical history of heart disease and a normal EKG or an ejection fraction measured by echocardiogram or MUGA scan of at least 45%.
- Transaminase less than twice the upper limit of normal. Bilirubin <1.5 mg%.
- Serum creatinine ≤2.0 mg/dL. Patients presenting with obstructive uropathy may be eligible if they show excellent response to nephrostomy drainage.
- Absolute neutrophil count ≥1500; platelet count ≥100,000.

3.1.4. Patients must not have had any previous systemic chemotherapy for bladder cancer, including neoadjuvant or adjuvant treatment given remotely. Gemcitabine/cisplatin is the standard of care for metastatic urothelial cancer. Patients who have received treatment would be either resistant or refractory to additional doses. In addition, they would have residual adverse effects from treatment and would be particularly susceptible to further neuropathic adverse events. Any prior intravesicular therapy is allowed.

3.1.5. Women of childbearing potential must have a negative pregnancy test prior to starting therapy. Men and women of childbearing potential must be willing to consent using effective contraceptive while on treatment and for a reasonable period thereafter.

3.1.6. Patients must not have an active, or likely to become active, second malignancy.

3.1.7. Patients must be at least 6 weeks out from pelvic irradiation, and must not have had more than 10% of the bone marrow irradiated.

3.2 Exclusion Criteria

3.2.1. Patients with uncontrolled CNS metastasis are not eligible.

3.2.2. Patients with a history of peripheral neuropathy greater than grade 1 are not eligible.

3.2.3. Pregnant women are excluded.

4.0 TREATMENT PLAN

4.1 Patients will be registered in the Genitourinary Oncology Program.

4.2 Combination chemotherapy consisting of gemcitabine and cisplatin plus paclitaxel.

4.3 The treatment will be repeated on a 21-day cycle. Patients will receive therapy in the Genitourinary Oncology Infusion Center or as an inpatient.

4.4 The gemcitabine will be administered as an IV infusion over 10mg/m2/min. The paclitaxel will be administered as an IVPB over 3 hours. The cisplatin will be administered as an IVPB over 2 hours.

4.5 Premedication for the gemcitabine infusion will consist of ondansetron 8 mg IV.

4.6 Premedication for the paclitaxel and cisplatin infusion will consist of dexamethasone 12 mg IV, ondansetron 8 mg IV, and diphenhydramine 25-50 mg IV.

4.7 Treatment Group:

Level	Gemcitabine (mg/m^2) Days 1, 8	Paclitaxel (mg/m^2) Day 2	Cisplatin (mg/m^2) Day 2
-2	800	135	70
-1	1000	135	70
0	1000	175	70

4.8 Dose modification will occur only for paclitaxel or gemcitabine. The dose modifications will be based on Grade 4 hematologic toxicity. The modifications will occur consistent with section 4.7.

For granulocyte counts <500 cells/µL over 96 hours, filgrastim 5 µg/kg/day will be administered subcutaneously, daily for 3 days or until granulocyte is 1000 cells/mm^3. For subsequent cycles, if granulocytopenia persists with filgrastim therapy, treatment dose will be decreased by 1 treatment level. Patients unable to tolerate treatment level -2 will be removed from the study.

For platelet count <25,000 cells/m^3 over 96 hours, treatment dose will be decreased by 1 treatment level for subsequent cycles. Patients unable to tolerate treatment level -2 will be removed from the study.

For hemoglobin <8 g/dL, patients will be transfused with packed red blood cells to maintain a hemoglobin of 8 g/dL. For non-symptomatic patients with hemoglobin between 8 and 9.9 g/dL who have adequate iron stores, epoetin alfa will be administered at a dose of 40,000 units subcutaneously once weekly.

4.9 Dose modifications based on non-hematologic toxicity. The following dose modification will be consistent with section 4.7. If grade 3/4 stomatitis occurs or bilirubin greater than the upper limits of normal, and alkaline phosphatase greater than 5 times the upper limit of normal, or an SGOT/SGPT greater than 5 times the upper limit of normal; grade 2 neuropathy (treatment with paclitaxel will be discontinued for grade 3/4 neuropathy).

4.10 Since all of the drugs in this trial are standard of care, there may be instances when subjects will receive their treatment at other infusion centers as well as their standard blood draws due to insurance network provider determinations, cost, etc. Dr. Amato will work closely with referring physicians and infusion centers. The lab results and clinic/infusion notes will be obtained and reviewed by Dr. Amato. All subjects will still come to the cancer center for restaging study visits.

5.0 PRETREATMENT EVALUATION

5.1 All patients must have an appropriate history and physical examination. Specific details to be recorded include the date of original diagnosis, the date of the first documentation of muscle-invasive disease, prior intravesical therapies (if any), results of -staging‖ studies at the time of initiation of systemic therapy (see below). The physical examination must include current height and weight; the presence or absence of pathologic adenopathies, the results of cardiovascular examination, including: the presence or absence of carotid or iliac bruits, an assessment of peripheral pulses and the presence or absence of peripheral edema; examination of the oral cavity; and palpation of the inguinal nodes, abdomen and rectal examination.

5.2 All patients must have a complete blood count (including a differential and platelet count), alkaline phosphatase, electrolytes, calcium, phosphorous, magnesium, BUN, albumin, total protein, bilirubin, transaminase (either SGOT or SGPT), glucose, creatinine, CEA, beta-hCG, beta-2 microglobulin, and CA-125 within 3 weeks of study entry. All patients will have a bone scan and x-ray or CT scan of the chest, abdomen and pelvis within one month of study entry. An EKG within 3 months must be available. In addition, if a baseline measurement of ejection fraction (EF) is required, this should be obtained within 3 months of study entry.

6.0 EVALUATION DURING STUDY

These assessments should be performed within ±3 days of the scheduled day of assessment. Schedule of Assessments can be found in Appendix D.

6.1 All patients will have a clinical assessment every 3 weeks. Data on symptom status, pain medication use and acute accumulative toxicity will be recorded.

6.2 All patients will have a weekly CBC for the first 6 weeks of therapy. Following this, the frequency of CBC monitoring can be tailored in light of the experience during the first 6 weeks of therapy.

6.3 All patients will have a weekly complete metabolic panel for the first 6 weeks of therapy. Following this, the frequency of complete metabolic profile monitoring can be tailored in light of the experience during the first 6 weeks of therapy.

6.4 Patients with elevated tumor markers at study entry should have these repeated at the six-week clinical evaluations, even if they normalize.

6.5 Whatever imaging is required to assess response in at least one measurable disease site should be repeated at the first six-week clinical evaluation. If a patient meets criteria for response (see 7.0 below), then all measurable sites of disease should be imaged when the patient returns for evaluation after 12 weeks on the same therapy.

7.0 CRITERIA FOR EVALUATION, ENDPOINT DEFINITIONS AND REMOVAL FROM STUDY

Tumor response will be determined according to the Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1.

8.0 SAFETY MONITORING AND REPORTING

The investigator will monitor each patient for clinical and laboratory evidence of adverse events on a routine basis throughout the study following the NCI Common Terminology Criteria for Adverse Events (CTCAE), Version 4.0. A link to the electronic version of the CTCAE can be found in Appendix A. Investigators must document their review of laboratory reports by initialing and dating each report, as well as addressing the clinical significance (for significant abnormalities). The investigator will assess and record any adverse event (serious and non-serious) in detail on the adverse event form including the date of onset, description, severity, time course, duration, outcome and relationship to the study drug from the time the patient signs the informed consent until 4 weeks after the patient has stopped study treatment.

8.1 Adverse Events

All adverse events should be treated appropriately. Such treatment may include interruption or discontinuation of study drug, starting or stopping concomitant treatments, changes in the frequency or nature of assessments, hospitalization, or any other medically required intervention.

Information about common side effects already known about the study drug can be found in the protocol and respective package inserts. This information will be included in the patient informed consent and should be discussed with the patient during the study as needed.

8.2 Adverse Event Definition

An adverse event (AE) is defined as any unintended or undesirable, noxious, or pathological change, compared to pre-existing conditions, experienced by a patient during a clinical study or the follow-up period, regardless of relationship to study drug. Adverse events include:

- Suspected adverse drug reactions.
- Reactions from drug overdose, abuse, withdrawal, sensitivity, or toxicity.
- Significant changes or abnormalities, when compared to baseline, in structure (sign), function (symptom), clinical laboratory results, or physiological testing. This includes any worsening of a pre-existing condition temporally associated with the use of study drug.
- Other medical events, regardless of their relationship to the study drug, such as injury, surgery, accidents, extensions of symptomatology, or apparently unrelated illnesses.

8.3 Evaluating Adverse Events

Each adverse event will be evaluated to determine:

- the severity grade (mild, moderate, severe) or (grade 1-4)
- its relationship to the study drug(s) (suspected/not suspected)
- its duration (start and end dates or if continuing at final exam)
- action taken (no action taken; study drug dosage adjusted/temporarily interrupted; study drug permanently discontinued due to this adverse event; concomitant medication taken; non-drug therapy given; hospitalization/prolonged hospitalization)
- outcome
- whether it constitutes a serious adverse event (SAE)

8.4 Determination of Severity

The severity of AEs will be assessed according to CTCAE, Version 4.0. If the AE is not defined in the CTCAE, the Investigator will determine the severity of an adverse event based on the following definitions:

- Mild (Grade 1): The AE is noticeable to the patient but does not interfere with routine activity. The AE does not require discontinuing administration or reducing the dose of the study drug.
- Moderate (Grade 2): The AE interferes with routine activity but responds to symptomatic therapy or rest. The AE may require reducing the dose but not discontinuing administration of the study drug.
- Severe (Grade 3): The AE significantly limits the patient‘s ability to perform routine activities despite symptomatic therapy. In addition, the AE leads to discontinuing administration or reducing the dose of the study drug.
- Life-Threatening (Grade 4): The AE requires discontinuing administration of the study drug. The patient is at immediate risk of death.

8.5 Determination of Relatedness

The Investigator will determine the relatedness of an adverse event with the study drug based on the following definitions:

Not Related

This category applies to those adverse events which, after careful medical consideration, are felt to be due to extraneous causes (disease, environment, etc.) that are not related to the administration of study drug.

Probably Not Related (must have first two bullets below)
This category applies to those adverse events, which, after careful medical consideration, are clearly felt unlikely to be related to the administration of the study drug. The relation- ship of an adverse event to the study drug can be considered probably not related if:

- It does not follow a reasonable temporal sequence from administration of the drug.
- It could readily have been a result of the patient's clinical state, environmental or toxic factors, or other modes of therapy administered to the patient.
- It does not follow a known response pattern to the suspected drug.
- It does not reappear or worsen when the drug is readministered.

Possibly Related (must have first two bullets below)
This category applies to those adverse events, which, after careful medical consideration, are felt unlikely to be related to the administration of the study drug, but the possibility cannot be ruled out with certainty. The relationship of an adverse event to the study drug can be considered possibly related if:

- It follows a reasonable temporal sequence from administration of the drug.
- It could readily have been a result of the patient's clinical state, environmental or toxic factors, or other modes of therapy administered to the patient.
- It follows a known response pattern to the suspected drug.

Probably Related (must have first three bullets below)
This category applies to those adverse events which, after careful medical consideration, are felt with a high degree of certainty to be related to the administration of the study drug. The relationship of an adverse event to the study drug can be considered probably related if:

- It follows a reasonable temporal sequence from administration of the drug.
- It could not be reasonably explained by the known characteristics of the patient's clinical state, environmental or toxic factors or other modes of therapy administered to the patient.
- It disappears or decreases upon cessation of drug or reduction in dose.*
- It follows a known response pattern to the suspected drug.

Definitely Related (must have first three bullets below)
This category applies to those adverse events, which, after careful medical consideration, are felt to be related to the administration of the drug. The relationship of an adverse event to the study drug can be considered definitely related if:

- It follows a reasonable temporal sequence from administration of the drug or drug levels have been established in body fluids or tissues.
- It could not be reasonably explained by the known characteristics of the patient's clinical state, environmental or toxic factors or other modes of therapy administered to the patient.
- It disappears or decreases upon cessation of drug or reduction in dose and, if applicable, appears upon rechallenge.*
- It follows a known response pattern to the suspected drug.

*There are exceptions when an adverse event does not disappear upon discontinuation of the drug, yet drug relatedness clearly exists; e.g., 1) tardive dyskinesia, 2) fixed drug eruptions.

8.6 Serious Adverse Events

Information about all serious adverse events (SAEs) will be collected and recorded. A SAE is an undesirable sign, symptom or medical condition which:

- is fatal or life-threatening
- results in persistent or significant disability/incapacity
- constitutes a congenital anomaly/birth defect
- requires inpatient hospitalization or prolongation of existing hospitalization, unless hospitalization is for:
  - routine treatment or monitoring of the studied indication, not associated with any deterioration in condition (specify what this includes)
  - elective or pre-planned treatment for a pre-existing condition that is unrelated to the indication under study and has not worsened since the start of study drug
  - treatment on an emergency outpatient basis for an event not fulfilling any of the definitions of a SAE given above and not resulting in hospital admission
  - social reasons and respite care in the absence of any deterioration in the patient‘s general condition
- is medically significant, i.e., defined as an event that jeopardizes the patient or may require medical or surgical intervention to prevent one of the outcomes listed above

8.7 SAE Reporting

The principal investigator has the obligation to report all serious adverse events to the IRB, DSMB and FDA according to their respective requirements. All events reported to the FDA by the investigator are to be filed utilizing the Form FDA 3500A (MedWatch Form).

Serious Adverse Events (SAE) that are determined by the PI to be unexpected + related will be submitted to the DSMB within 7 calendar days of the determination by telephone or fax; written report no later than 15 calendar days of the determination. Deaths should be reported to the IRB within 24 hours of investigator knowledge. Any unexpected, serious, related adverse experiences should be reported to the IRB within 7 calendar days of investigator knowledge.

Any pregnancy that occurs during study participation should be reported. The pregnancy should be followed up to determine outcome, including spontaneous or voluntary termination, details of birth, and the presence or absence of any birth defects, congenital abnormalities or maternal and newborn complications.

8.8 Unanticipated Problem Reporting

The Principal Investigator (PI) must notify the IRB of unexpected problems that might arise during the study within 7 days. The PI must make a judgment call regarding the expectedness and causality of the problem. Examples include:

- any adverse event which in the opinion of the PI is both unexpected and related and places patients or others at risk of harm

- Protocol deviation that harmed patients or placed patients in increased risk of harm
- Unanticipated adverse device effect
- A breach of confidentiality
- Change in FDA labeling or withdrawal from marketing of a drug, device, or biologic used in a research protocol
- Information that indicates a change to the risks or potential benefits of the research

9.0 STATISTICAL CONSIDERATIONS

The primary efficacy endpoint was the objective response rate—that is, the proportion of patients achieving either a CR or a PR at any time during the study. Responses (CR, PR, PD, and SD) will be evaluated according to RECIST 1.1 criteria (see Appendix C). Simon's one-sample two-stage design will be used. Our null hypothesis is that the response rate is 50%, and our alternative hypothesis is that the response rate is 70%. In the first stage, 23 patients will be accrued. If ≤12 patients of the first 23 are assessable for responses, the study will be stopped early for futility. If ≥13 responses are observed in the first stage, accrual will continue for a total of 37 patients. If ≥23 responses are observed in 37 patients by the end of stage two, we will conclude that the treatment is warranted for further investigation. This design will yield a one-sided type I error rate of 0.05 and power of 80%. There will be no comparison group.

An interim safety analysis is planned after 3 patients and again after 12 patients have completed 1 cycle of treatment. During this analysis, enrollment will be stopped, the DSMB will review the safety and toxicity information and make their recommendation, and the DSMB report will be given to the IRB for review prior to treatment of additional patients.

In a secondary analysis, we will also assess progression-free and overall survival to determine the potential benefit of the study regimen. Descriptive statistics will be used for this analysis.

Toxicity assessment will be observational. Numbers and types of events will be quantified, graded according to CTCAE, and reported in a summary table.

10.0 DATA AND PROTOCOL MANAGEMENT

10.1 Protocol Compliance

Written informed consent must be obtained from the patient prior to study specific screening tests or procedures. Results of all baseline evaluations which assure that all inclusion and exclusion criteria have been satisfied, must be reviewed by the Investigator prior to enrollment of that patient. All required interim and pre-treatment data should be available and the investigator must have made a designation as to tumor response and toxicity grade.

10.2 Data Collection

Investigators or their designee must enter the data required by the protocol onto Case Report Forms (CRFs). A brief explanation for required but missing data should be recorded as a com-

ment. The Principal Investigator is ultimately responsible for assuring that data entered into the CRFs are accurate, authentic / original, attributable, complete, consistent, legible, timely (contemporaneous), enduring and available when required.

Entries made in the CRF must be either verifiable against source documents, or have been directly entered into the CRF, in which case the entry in the CRF will be considered as the source data. Any corrections to entries made in the CRFs or source documents must be dated, initialed and explained (if necessary) and should not obscure the original entry. The Investigator will sign the CRFs to indicate that, to his/her knowledge, they are complete and accurate.

10.3 Database Management

The data manager will review the CRF data entered by study staff for completeness and accuracy. Data queries stating the nature of the problem and requesting clarification will be created for discrepancies and missing values and sent to the study coordinator. The study coordinator will respond promptly to queries and make any necessary changes to the CRFs.

10.4 Site Monitoring

To ensure that the protocol and Good Clinical Practices (GCP) are being followed and that study data are accurate, complete and reliable, the trial will be monitored by a Data Safety Monitoring Board (DSMB), Medical Monitor and CRA monitoring as specified in the Data Safety Monitoring Plan (DSMP) for the study and the DSMB's charter.

11.0 ETHICAL CONSIDERATIONS

11.1 Ethical Compliance

The study will be conducted in accordance with legal and regulatory (21 CFR 50, 56, 312 as applicable) requirements, as well as the general principles set forth in the Guidelines for GCP (ICH 1996) and the Declaration of Helsinki (World Medical Association 1996 and 2008).

The principal investigator is responsible for ensuring that all participating staff members are adequately trained and competent to perform his/her assigned tasks.

11.2 IRB Review

Before implementing this study, the protocol, the proposed informed consent form, and other required information, must be reviewed and approved by a properly constituted Institutional Review Board (IRB). Any amendments to the protocol, other than administrative ones, must be re-viewed and approved by this committee before implementation. If an immediate change to the protocol is implemented for safety reasons by the investigator, the IRB must be informed immediately. The study must be reviewed and approved at least annually as well.

11.3 Recruitment

Recruitment typically occurs from patients treated at the Cancer Center. Recruitment may occur from patient self-referral from trials posted on ClinicalTrials.gov. If the investigator wishes to expand recruitment, advertisements will be reviewed and approved by the IRB prior to use.

11.4 Informed Consent

The Investigator will be responsible for obtaining consent, documented on the Informed Consent Form (ICF) signed and dated by each patient or his/her legally authorized repre-

sentative, prior to his/her participation in the study, in accordance with ICH GCP guidelines. The ICF will be written in non-technical language. The patient should read and be given as much time as they need to consider their participation before signing and dating it.

The investigator or study staff designee must explain to each patient the nature of the study, its purpose, the procedures involved, the expected duration, the potential risks and benefits involved and any discomfort it may entail. Each patient must be informed that participation in the study is voluntary and that he/she may withdraw from the study at any time and that withdrawal of consent will not affect his/her subsequent medical treatment or relationship with the treating physician.

Participation in the study and date of informed consent should be documented appropriately in the patient‘s files. The original ICF will be maintained in the research files and a copy must be maintained in the institution‘s medical records. The patient or his/her legally authorized representative will also be given a copy of the signed consent form.

11.5 Confidentiality

All records identifying the patient will be kept confidential and, to the extent permitted by the applicable laws and/or regulations, will not be made publicly available. Patient names will not be supplied to third parties. A unique study accession number will be assigned to each patient on study and will be used on the CRFs. Identifiable data on any document (e.g., pathologist report) must be redacted before a copy of the document is supplied to third parties. The study coordinator will maintain a list to enable patients‘ records to be identified for verification purposes.

Study data stored electronically will be stored in zone 100, on password-protected, encrypted computers. Paper study data will be maintained by the study coordinator in the locked research offices.

11.6 Publication of Study Results

The investigator will assure that the key elements of this protocol will be posted in a publicly accessible database such as www.ClinicalTrials.gov. In addition, upon study completion and finalization of the study report the results of this study will be submitted for publication in scientific journals and/or scientific meetings. If the results of the study are published, the patient‘s identity will remain confidential.

11.7 Retention of Documents

To enable evaluations and/or audits from regulatory authorities or sponsors, the investigator agrees to keep records, including the identity of all participating patients (sufficient information to link records, e.g., CRFs and hospital records), all original signed informed consent documents, copies of all CRFs, safety reporting forms, source documents, detailed records of treatment dis-position, and adequate documentation of relevant correspondence in a secure storage facility.

Essential documents (written and electronic) should be retained for at least three (3) years after the completion of the study. The records should be retained by the investigator according to local regulations or as specified in the Clinical Study Agreement (CSA), whichever is longer.

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APPENDIX A: NCI Common Terminology Criteria for Adverse Events

Safety and tolerability will be assessed according to Version 4.0 of the National Cancer Institute's Common Terminology Criteria for Adverse Events (CTCAE). An electronic version may be found at: http://ctep.cancer.gov/reporting/ctc.html.

In brief:

Grade refers to the severity of the AE. The CTCAE displays Grades 1 through 5 with unique clinical descriptions of severity for each AE based on this general guideline:

Grade 1 Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
Grade 2 Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL*.
Grade 3 Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self care ADL**.
Grade 4 Life-threatening consequences; urgent intervention indicated.
Grade 5 Death related to AE.

A Semi-colon indicates 'or' within the description of the grade. A single dash (-) indicates a grade is not available.

Activities of Daily Living (ADL)

*Instrumental ADL refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.
**Self-care ADL refer to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden.

APPENDIX B: ECOG Performance Status

Grade	ECOG
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work
2	Ambulatory and capable of all selfcare but unable to carry out any work activities. Up and about more than 50% of waking hours
3	Capable of only limited selfcare, confined to bed or chair more than 50% of waking hours
4	Completely disabled. Cannot carry on any selfcare. Totally confined to bed or chair
5	Dead

APPENDIX C: RECIST 1.1 Guidelines

Tumor response and progression will be defined according to RECIST 1.1 criteria. Electronic guidelines may be found at: http://www.eortc.be/recist/documents/RECISTGuidelines.pdf.

Response Evaluation Criteria in Solid Tumors (RECIST) Quick Reference:

Eligibility

- Only patients with measurable disease at baseline should be included in protocols where objective tumor response is the primary endpoint.

  Measurable disease - the presence of at least one measurable lesion. If the measurable disease is restricted to a solitary lesion, its neoplastic nature should be confirmed by cytology/histology.

  Measurable lesions - lesions that can be accurately measured in at least one dimension with longest diameter ≥20 mm using conventional techniques or ≥10 mm with spiral CT scan.

  Non-measurable lesions - all other lesions, including small lesions (longest diameter <20 mm with conventional techniques or <10 mm with spiral CT scan), i.e., bone lesions, leptomeningeal disease, ascites, pleural/pericardial effusion, inflammatory breast disease, lymphangitis cutis/pulmonis, cystic lesions, and also abdominal masses that are not confirmed and followed by imaging techniques; and.
- All measurements should be taken and recorded in metric notation, using a ruler or calipers. All baseline evaluations should be performed as closely as possible to the beginning of treatment and never more than 4 weeks before the beginning of the treatment.
- The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during follow-up.
- 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, documentation by color photography, including a ruler to estimate the size of the lesion, is recommended.

Methods of Measurement

- 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 10 mm or less in slice thickness contiguously. Spiral CT should be performed using a 5 mm contiguous reconstruction algorithm. This applies to tumors of the chest, abdomen and pelvis. Head and neck tumors and those of extremities usually require specific protocols.

- Lesions on chest X-ray are acceptable as measurable lesions when they are clearly defined and surrounded by aerated lung. However, CT is preferable.

- When the primary endpoint of the study is objective response evaluation, ultrasound (US) 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. US might also be useful to confirm the complete disappearance of superficial lesions usually assessed by clinical examination.

- The utilization of endoscopy and laparoscopy for objective tumor evaluation has not yet been fully and widely validated. Their uses in this specific context require sophisticated equipment and a high level of expertise that may only be available in some centers. Therefore, the utilization of such techniques for objective tumor response should be restricted to validation purposes in specialized centers. However, such techniques can be useful in confirming complete pathological response when biopsies are obtained.

- Tumor markers alone cannot be used to assess response. If markers are initially above the upper normal limit, they must normalize for a patient to be considered in complete clinical response when all lesions have disappeared.

- Cytology and histology can be used to differentiate between PR and 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).

Baseline documentation of "Target" and "Non-Target" lesions

- All measurable lesions up to a maximum of five lesions per organ and 10 lesions in total, representative of all involved organs should be identified as target lesions and recorded and measured at baseline.
- Target lesions should be selected on the basis of their size (lesions with the longest diameter) and their suitability for accurate repeated measurements (either by imaging techniques or clinically).
- A sum of the longest diameter (LD) for all target lesions will be calculated and reported as the baseline sum LD. The baseline sum LD will be used as reference by which to characterize the objective tumor.
- All other lesions (or sites of disease) should be identified as non-target lesions and should 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.

Response Criteria

	Evaluation of target lesions
* Complete Response (CR):	Disappearance of all target lesions
* Partial Response (PR):	At least a 30% decrease in the sum of the LD of target lesions, taking as reference the baseline sum LD
* Progressive Disease (PD):	At least a 20% increase in the sum of the LD of target lesions, taking as reference the smallest sum LD recorded since the treatment started or the appearance of one or more new lesions
* Stable Disease (SD):	Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum LD since the treatment started
	Evaluation of non-target lesions
* Complete Response (CR):	Disappearance of all non-target lesions and normalization of tumor marker level
* Incomplete Response/Stable Disease (SD):	Persistence of one or more non-target lesion(s) or/and maintenance of tumor marker level above the normal limits

* Progressive Disease (PD):	Appearance of one or more new lesions and/or unequivocal progression of existing non-target lesions (1)

(1) Although a clear progression of -non target‖ lesions only is exceptional, in such circumstances, the opinion of the treating physician should prevail and the progression status should be confirmed later on by the review panel (or study chair).

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

Target lesions	Non-Target lesions	New Lesions	Overall response
CR	CR	No	CR
CR	Incomplete response/SD	No	PR
PR	Non-PD	No	PR
SD	Non-PD	No	SD
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD

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

Confirmation

- The main goal of confirmation of objective response is to avoid overestimating the response rate observed. In cases where confirmation of response is not feasible, it should be made clear when reporting the outcome of such studies that the responses are not confirmed.
- To be assigned a status of PR or CR, changes in tumor measurements must be confirmed by repeat assessments that should be performed no less than 4 weeks after the criteria for response are first met. Longer intervals as determined by the study protocol may also be appropriate.
- In the case of SD, follow-up measurements must have met the SD criteria at least once after study entry at a minimum interval (in general, not less than 6-8 weeks) that is defined in the study protocol

Duration of overall response

- The duration of overall response is measured from the time measurement criteria are met for CR or PR (whichever status is recorded first) until the first date that recurrence or PD is objectively documented, taking as reference for PD the smallest measurements recorded since the treatment started.

Duration of stable disease

- SD 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.
- The clinical relevance of the duration of SD varies for different tumor types and grades. Therefore, it is highly recommended that the protocol specify the minimal time interval required between two measurements for determination of SD. This time interval should take into account the expected clinical benefit that such a status may bring to the population under study.

Response review

- For trials where the response rate is the primary endpoint it is strongly recommended that all responses be reviewed by an expert(s) independent of the study at the study‘s completion. Simultaneous review of the patients‘ files and radiological images is the best approach.

Reporting of results

- All patients included in the study must be assessed for response to treatment, even if there are major protocol treatment deviations or if they are ineligible. Each patient will be assigned one of the following categories: 1) complete response, 2) partial response, 3) stable disease, 4) progressive disease, 5) early death from malignant disease, 6) early death from toxicity, 7) early death because of other cause, or 9) unknown (not assessable, insufficient data).
- All of the patients who met the eligibility criteria should be included in the main analysis of the response rate. Patients in response categories 4-9 should be considered as failing to respond to treatment (disease progression). Thus, an incorrect treatment schedule or drug administration does not result in exclusion from the analysis of the response rate. Precise definitions for categories 4-9 will be protocol specific.
- All conclusions should be based on all eligible patients.
- Subanalyses may then be performed on the basis of a subset of patients, excluding those for whom major protocol deviations have been identified (e.g., early death due to other reasons, early discontinuation of treatment, major protocol violations, etc.). However, these subanalyses may not serve as the basis for drawing conclusions concerning treatment efficacy, and the reasons for excluding patients from the analysis should be clearly reported.
- The 95% confidence intervals should be provided.

APPENDIX D: Schedule of Assessments

Protocol Activity	Pretreat-ment timeframe	Cycle 1				Cycle 2				Subsequent Cycles			
Visit Name		**C1 D1**	**C1 D2**	**C1 D8**	**C1 D15**	**C2 D1**	**C2 D2**	**C2 D8**	**C2 D15**	**C3-6 D1**	**C3-6 D2**	**C3-6 D8**	**C4,6 D15**
Informed consent	-21 to -1												
Documentation of histologic di-agnosis and extent of cancer	-21 to -1												
Inclusion/Exclusion criteria	-21 to -1												
History & Physical exam with height and weight	-7 to -1												X
Interim physical assessment with AEs, con meds, and toxicity						X				X			
ECOG Performance status	-7 to -1									X			X
CBC with diff, plts*	-21 to -1	X		X	X	X		X	X	X*			X
Comprehensive metabolic panel*	-21 to -1	X		X	X	X		X	X	X*			X
Electrolytes*	-21 to -1	X		X	X	X		X	X	X*			X
Beta 2 microglobulin	-21 to -1								X	X**			X
Beta HCG	-21 to -1								X	X**			X
CEA	-21 to -1								X	X**			X
CA-125	-21 to -1								X	X**			X
CT or x-ray of Chest, Abdomen and Pelvis with RECIST tumor measurements	-28 to -1								X	X***			X***
Bone Scan	-28 to-1								X	X***			X***
12 Lead EKG	-90 to +3												
Echo or MUGA Scan	-90 to +3												
Chemotherapy (Gemcitabine)		X		X		X		X		X		X	
Chemotherapy (Cisplatin, Pacli-taxel)			X				X				X		

*Follow-up frequency of monitoring after the first 6 weeks to be tailored based on the first 6 weeks of therapy.
**Subjects with elevated tumor markers at study entry should have them repeated every 6 weeks.
***Whatever imaging is required to assess response in at least 1 measurable disease site should be repeated at the first 6-week evaluation. If subject meets crite-ria for response, all measurable sites of disease should be reimaged after 12 weeks of therapy.