

**Phase II Trial of Gemcitabine, Cisplatin, plus Ipilimumab as First-line
Treatment for Patients with Metastatic Urothelial Carcinoma**
Hoosier Cancer Research Network GU10-148

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PROTOCOL SIGNATURE PAGE

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I confirm I have read this protocol, I understand it, and I will work according to this protocol and to the ethical principles stated in the latest version of the Declaration of Helsinki, the applicable guidelines for good clinical practices, or the applicable laws and regulations of the country of the study site for which I am responsible, whichever provides the greater protection of the individual. I will accept the monitor's overseeing of the study. I will promptly submit the protocol to applicable ethical review board(s).

Instructions to the investigator: Please **SIGN** and **DATE** this signature page. **PRINT** your name and title, the name and location of the facility in which the study will be conducted, and the expected IRB approval date. Scan and email the completed form to Hoosier Cancer Research Network and keep a record for your files.

Signature of Investigator

Date

Investigator Name (print or type)

Investigator Title

Name of Facility

Location of Facility (City and State)

Expected IRB Approval Date

☐ Not Submitting to IRB

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STUDY SYNOPSIS**Hoosier Cancer Research Network Protocol: GU10-148**

TITLE	Protocol title: Phase II Trial of Gemcitabine, Cisplatin, plus Ipilimumab as First-line Treatment for Patients with Metastatic Urothelial Carcinoma
STUDY PHASE	Phase II
OBJECTIVES	<p><u>Primary Objective:</u></p> <ul style="list-style-type: none"> To determine the 1-year overall survival of patients with advanced/metastatic urothelial carcinoma treated with gemcitabine, cisplatin, plus ipilimumab. <p><u>Secondary Objective:</u></p> <ul style="list-style-type: none"> To determine the progression-free survival (using immune-related response criteria [irRC]) of patients with advanced/metastatic urothelial carcinoma treated with gemcitabine, cisplatin, and ipilimumab. To determine the disease control rate (complete response + partial response + stable disease using irRC and Response Evaluation Criteria In Solid Tumors [RECIST] v1.0 [see Section 8.2]) to treatment with gemcitabine, cisplatin, plus ipilimumab. To determine the safety of treatment with gemcitabine, cisplatin, plus ipilimumab. <p><u>Exploratory Objectives:</u></p> <ul style="list-style-type: none"> To serially monitor the global composition immune cells in the blood by polychromatic flow cytometry and correlate changes with clinical outcome. To determine the frequency of tumor-antigen specific CD8+ T cells by antigen-specific multi-cytokine production (IFN-γ, TNF-α and IL-2) by intracellular cytokine staining. To perform transcriptional profiling of blood samples before and after treatment using microarray and correlate changes with clinical outcomes.
STUDY DESIGN	<p>Treatment during the “induction” phase will be administered in six 21-day cycles. During cycles 1 and 2, gemcitabine plus cisplatin will be administered WITHOUT ipilimumab. During cycles 3-6, combination therapy with gemcitabine, cisplatin, plus ipilimumab will be administered. Patients without evidence of disease progression (by irRC) after completion of cycle 6 will continue single-agent ipilimumab “maintenance” every 3 months.</p> <p>Induction</p> <p>Patients will undergo a restaging CT scan after cycle 2 and after cycle 6. However, patients with evidence of disease progression (in the absence of significant functional/symptomatic deterioration) on the post-cycle 2 CT scan will not be required to come off study as they will have not yet started ipilimumab. Patients may elect to come off study at any time.</p>

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Furthermore, as durable disease stabilization and/or objective tumor response can be seen in other advanced solid tumors after early progression before 12 weeks of ipilimumab treatment, it is recommended that, in the absence of treatment-limiting toxicities (e.g., serious immune-related adverse events [irAEs]), all four doses of ipilimumab be administered over the initial 12 weeks even in the setting of apparent progression, providing the subject's performance status remains stable.

Based on clinical experience in ongoing and completed melanoma studies, the following recommendations apply for subject management in light of the post-cycle 6 or later tumor assessments:

- The appearance of new lesions in subjects with other stable or shrinking baseline tumor burden may be experiencing clinical benefit and should continue in follow-up and/or maintenance therapy before alternative anti-cancer agents are considered. These subjects can be seen to have continued tumor shrinkage in follow-up scans.
- As long as overall tumor burden is stable or decreasing, subjects should remain in follow-up and/or maintenance, even in the presence of new lesions.
- Clinical progression warranting alternative anti-cancer treatment should be considered only in subjects whose overall tumor burden appears to be substantially increased and/or in subjects whose performance status is decreased.

The irRC will be utilized which requires a confirmatory scan documenting progression²². The definition of confirmation of progression represents an increase in tumor burden $\geq 25\%$ compared with nadir at two consecutive time points at least 4 weeks apart. Therefore, patients with disease progression on the post-cycle 6 scan (in the absence of symptomatic/functional deterioration) should have a confirmatory CT scan at least 4 weeks later.

Maintenance

As per the schedule of dosing in the ongoing and completed clinical studies using ipilimumab in subjects with pretreated advanced melanoma, maintenance therapy should be offered to all subjects who have not experienced unacceptable toxicity (refractory Grade > 3 irAEs) and are considered by the investigator to be obtaining clinical benefit, either because of apparent tumor stability or continued shrinkage and/or late response.

A single dose of 10 mg/kg ipilimumab given intravenously over 90 minutes should be administered every 12 weeks, starting from approximately week 28 until the subject is no longer clinically benefiting from therapy, per the investigator, or until the occurrence of unacceptable or unmanageable toxicity.

Subjects in maintenance should receive radiographic tumor assessments every 12 weeks before administration. Subjects who continue to experience clinical benefit, as defined

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	by the investigator, and who have not experienced unacceptable toxicity (refractory Grade > 3 irAEs), are eligible to receive continued maintenance.
NUMBER OF PATIENTS	36
ELIGIBILITY	<ul style="list-style-type: none"> Written informed consent and HIPAA authorization for release of personal health information. <p>NOTE: HIPAA authorization may be included in the informed consent or obtained separately.</p> <ul style="list-style-type: none"> Age ≥ 18 years at the time of consent. Karnofsky performance status (KPS) $\geq 80\%$ within 7 days prior to registration for protocol therapy. Women of childbearing potential (WOCBP) must be using an adequate method of contraception to avoid pregnancy throughout the study and for up to 26 weeks after the last dose of investigational product, in such a manner that the risk of pregnancy is minimized. <p>WOCBP include any female who has experienced menarche and who has not undergone successful surgical sterilization (hysterectomy, bilateral tubal ligation, or bilateral oophorectomy) or is not post-menopausal. Post-menopause is defined as: Amenorrhea ≥ 12 consecutive months without another cause, or for women with irregular menstrual periods and taking hormone replacement therapy (HRT), a documented serum follicle-stimulating hormone (FSH) level ≥ 35 mIU/mL.</p> <p>Women who are using oral contraceptives, other hormonal contraceptives (vaginal products, skin patches, or implanted or injectable products), or mechanical products such as an intrauterine device or barrier methods (diaphragm, condoms, spermicides) to prevent pregnancy, or are practicing abstinence or where their partner is sterile (e.g., vasectomy) should be considered to be of childbearing potential.</p> <ul style="list-style-type: none"> WOCBP must have a negative serum or urine pregnancy test (minimum sensitivity 25 IU/L or equivalent units of HCG) within 72 hours before the start of ipilimumab. Men of fathering potential must be using an adequate method of contraception to avoid conception throughout the study [and for up to 26 weeks after the last dose of investigational product] in such a manner that the risk of pregnancy is minimized. Females must not be pregnant or breastfeeding. Histological or cytological proof of urothelial carcinoma of the urethra, bladder,

ureters, or renal pelvis.

- Advanced (clinical stage T4b, unresectable) or metastatic disease.
- No active CNS metastases. Subjects with neurological symptoms must undergo a head CT scan or brain MRI to exclude brain metastasis within 28 days of registration.

NOTE: A subject with prior brain metastasis may be considered if they have completed their treatment for brain metastasis, no longer require corticosteroids, and are asymptomatic

- No prior malignancy is allowed except for cancers that have been definitively treated with a risk of recurrence of < 30% based on the treating oncologist's assessment.
- Patients may not have received prior systemic chemotherapy for metastatic/advanced urothelial carcinoma.

NOTE: Prior neoadjuvant/adjuvant therapy is permitted if completed ≥ 12 months prior to registration for protocol therapy. Prior intravesical therapy is permitted.

- No treatment with any investigational agent within 30 days prior to registration for protocol therapy.
- Prior radiation therapy is allowed to < 25% of the bone marrow [see bone marrow radiation chart in the study procedure manual (SPM)].

NOTE: No radiation therapy within 30 days prior to registration for protocol therapy.

- Prior Autoimmune disease: Patients with a history of inflammatory bowel disease, including ulcerative colitis and Crohn's Disease, are excluded from this study, as are patients with a history of symptomatic disease (e.g., rheumatoid arthritis, systemic progressive sclerosis [scleroderma], systemic lupus erythematosus, autoimmune vasculitis [e.g., Wegener's granulomatosis]); motor neuropathy considered of autoimmune origin (e.g. Guillain-Barre Syndrome and Myasthenia Gravis).

NOTE: Patients with other immune disorders should not be enrolled without discussion with the principal investigator.

- No underlying medical or psychiatric condition, which in the opinion of the investigator will make the administration of ipilimumab hazardous or obscure the interpretation of adverse events (AEs), such as a condition associated with frequent diarrhea.
- No non-oncology vaccine therapy used for prevention of infectious diseases (for up

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to 1 month before or after any dose of ipilimumab).

- No history of prior treatment with ipilimumab or prior CD137 agonist or CTLA-4 inhibitor or agonist (See SPM for list of drugs).
- No known active or chronic infection with HIV, Hepatitis B, or Hepatitis C.
- No clinically significant infections as judged by the treating investigator.
- No chronic systemic corticosteroids (defined as the equivalent of prednisone ≥ 20 mg PO daily for > 6 months during the past year)

NOTE: Laboratory values must be obtained within 7 days prior to registration for protocol therapy.

- White blood cell count (WBC) $\geq 3.5K/mm^3$
- Hemoglobin (Hgb) ≥ 9 g/dL
- Platelets $\geq 100K/mm^3$
- Absolute neutrophil count (ANC) $\geq 1.5k/mm^3$
- Actual or Calculated creatinine clearance of ≥ 55 cc/min using the Cockcroft-Gault formula:

$$\text{Males: } \frac{(140 - \text{Age in years}) \times \text{Actual Body Weight in kg}}{72 \times \text{Serum Creatinine (mg/dL)}}$$

$$\text{Females: Estimated creatinine clearance for males} \times 0.85$$

- Bilirubin ≤ 1.5 times (\times) Upper Limit of Normal (ULN) (except patients with Gilbert's Syndrome, who must have a total bilirubin less than 3.0 mg/dL)
- Aspartate aminotransferase (AST) $\leq 2.5 \times \text{ULN}$. **NOTE:** If the patient has liver metastases present, then $\leq 5 \times \text{ULN}$
- Alanine aminotransferase (ALT) $\leq 2.5 \times \text{ULN}$. **NOTE:** If the patient has liver metastases present, then $\leq 5 \times \text{ULN}$
- Patient must consent to mandatory correlative sample collection.

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STATISTICAL CONSIDERATIONS	<p>though not a standard endpoint for a phase II trial, the current study will utilize 1 year overall survival as the primary endpoint. Given that late responses (and variable response patterns such as responses after documented progression) have occurred in patients with other solid tumors treated with ipilimumab, and given that the use of the irRC and timing of the scans in our study will bias progression-free survival endpoints, overall survival will provide the most definitive endpoint to consider the activity of the current regimen in the context of historical controls. The 1 year overall survival of patients treated with cisplatin and gemcitabine alone is 60%³.</p> <p>The primary objective is to estimate the 1 year overall survival (OS) rates for gemcitabine, cisplatin, plus ipilimumab. The sample size is calculated for a power level of 0.80, based on 90% one-sided confidence intervals (CI) calculated at the target rate of 80% for 1 year OS. We will recommend the regimen if lower bound of the resulting CI exceeds 60%. This is equivalent to testing the following hypothesis at Type I error level 0.10: H_0: 1-year overall survival rate \leq 60%, vs. H_a: 1-year overall survival rate $>$ 60%. For this purpose, we will enroll 36 subjects (inflating the sample size of 33 by 10% to account for potential missing data due to various reasons), assuming fewer than 20% of subjects will be off study before 1 year for various reasons (and thus with unknown survival status at 1 year). The sample size is determined from an upper bound for the Greenwood formula for the variance of Kaplan-Meier estimate at 1 year. All patients will be followed for at least 1 year from the enrollment. We expect an accrual rate of approximately 1-2 per month. This leads to approximately 17-34 months for accrual. With at least one year follow-up for the last subject, we expect the study to finish within approximately 2.5-3 years.</p> <p>The confidence interval of 1 year overall survival (OS) rates will be constructed based on Kaplan-Meier estimate. Response rates will be analyzed using statistical methods for binary outcomes. Progression-free survival and overall survival will be analyzed using log-rank test and Cox regression model. Association between immune-related adverse events and overall response rate will be tested using Fisher's exact test and Chi-square test.</p> <p>Potential biomarkers will be assessed by repeating the analysis of each clinical outcome with the level of each individual marker included as factor or covariate as appropriate. We will correlate outcomes with changes in the frequency of circulating immune cells, tumor antigen-specific CD8+ T cells, and whole blood transcriptional profiling before and after treatment. Significance of this association will be evaluated using the Chi-square test for binary outcomes and log-rank tests for time-to-event outcomes.</p> <p>The analysis population will be the group who receives at least one cycle of protocol therapy. Therefore, subjects who experience clinical deterioration and are removed from the study prior to cycle 3 (the first cycle with ipilimumab) will still be included in the analysis; however, based on prior studies of first-line therapy in patients with metastatic urothelial cancer, we expect this population to be very small. {Hahn, 2011 #1449} The starting point for survival analysis is the treatment (Gem+Cis) initiation date.</p> <p>An early stopping rule will be employed. If we are confident that more than 20% of</p>
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	<p>patients have experienced a nondermatologic immune-related adverse event of grade 3 or higher attributable to ipilimumab, that cannot be alleviated or controlled by appropriate care or corticosteroid therapy within 14 days after the initiation of supportive care or corticosteroid therapy, the study will close to further enrollment. We will therefore monitor the study when 5, 10, 20, and 30 patients have completed 6 cycles of treatment. We will continue enrollment while the toxicity evaluation is taking place (we will not halt enrollment for the analysis). The study regimen will be considered excessively toxic if we observe 3 or more out of 5, 4 or more out of 10, 6 or more out of 20, and 9 or more out of 30 patients. We will then stop the trial. These boundaries are determined from the lower bound of 80% exact binomial confidence intervals. See Section 12, Table 10 for the probabilities of stopping the trial due to this toxicity monitoring rule.</p>
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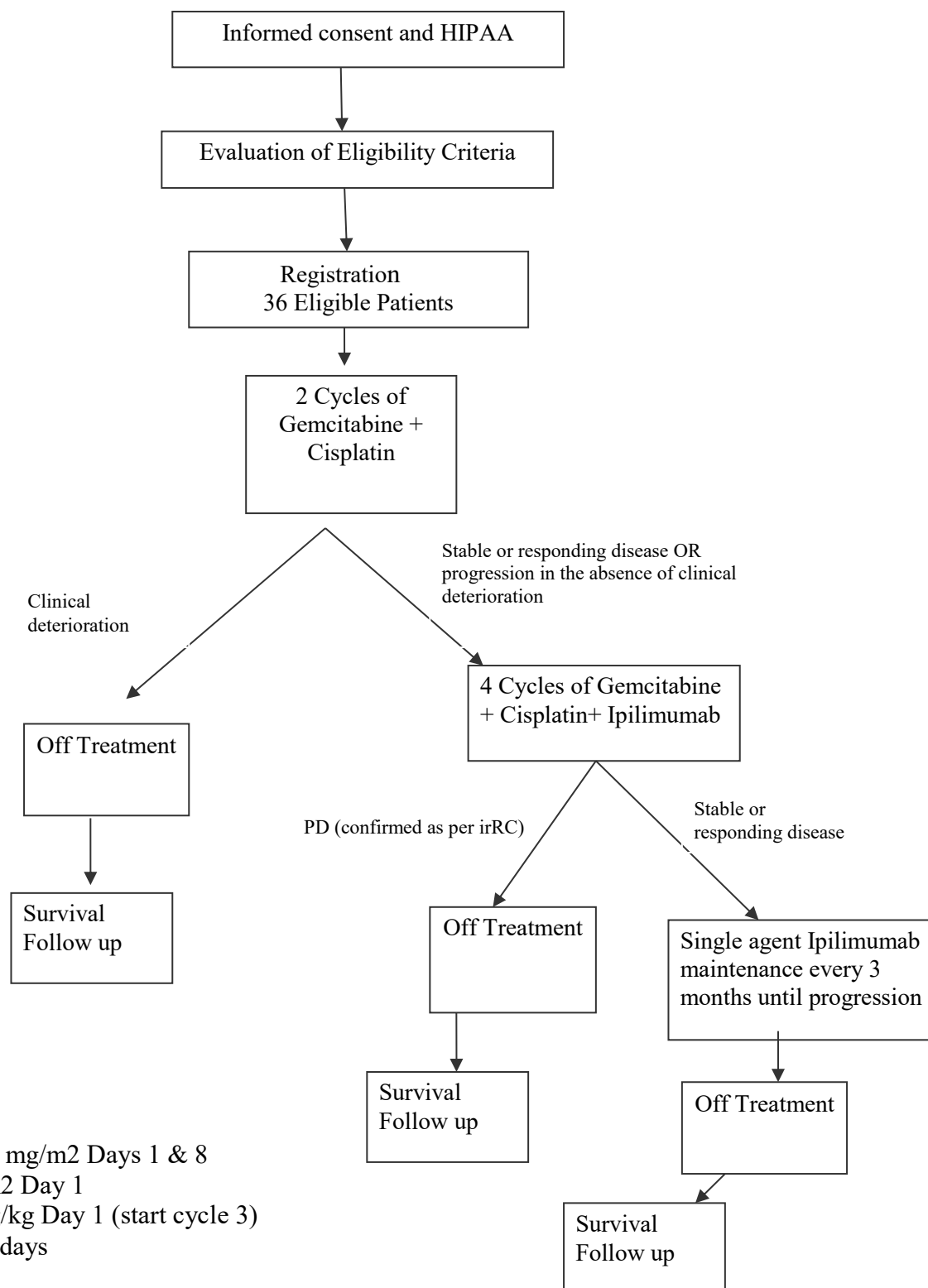
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SCHEMA

**Phase II Trial of Gemcitabine, Cisplatin, plus Ipilimumab as First-line Treatment for
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Gemcitabine 1000 mg/m² Days 1 & 8
Cisplatin 70 mg/m² Day 1
Ipilimumab 10 mg/kg Day 1 (start cycle 3)
Cycle length = 21 days

1.0 BACKGROUND & RATIONALE

Urothelial carcinoma of the urinary bladder is the second most common genitourinary malignancy. Each year in the United States, more than 60,000 patients will develop urothelial carcinoma and over 12,000 will die of their disease. While urothelial carcinoma is a chemosensitive neoplasm, current therapeutic approaches are inadequate. Response durations are short and the median survival of patients with metastatic disease is slightly over 1 year. These findings highlight the need for novel approaches to the treatment of metastatic urothelial carcinoma.

Chemotherapy is standard treatment for advanced bladder cancer. Cisplatin is among the most active agents in urothelial carcinoma and cisplatin-based combinations have long been the standards of care. The M-VAC (methotrexate, vinblastine, Adriamycin, and cisplatin) regimen, developed in the early 1980's, became a treatment standard based on data from two large randomized trials demonstrating improved survival with MVAC compared with single agent cisplatin or CISCA (cisplatin, Adriamycin, and cyclophosphamide), respectively ¹⁻². However, few patients achieved long-term survival with this regimen and severe treatment-related side effects were common.

In an attempt to improve the efficacy and tolerability of therapy for advanced urothelial carcinoma, various combinations of cisplatin with newer drugs have been explored. In a multicenter randomized phase III trial comparing gemcitabine and cisplatin (GC) with M-VAC in patients with advanced/metastatic urothelial carcinoma, 405 patients were enrolled ³. Both arms yielded similar response rates and overall survival (13.8 months with GC and 14.8 months with MVAC; HR 1.04; 95% CI, .82 – 1.32; $p=.75$). However, GC was associated with a better safety profile and improved tolerability. Given the results of this trial, GC has become a standard regimen for patients with metastatic urothelial carcinoma.

While the tolerability of treatment has improved over the past 20 years, efficacy has not. Novel approaches are clearly needed.

Bladder cancer is an immunogenic malignancy. Immunotherapy has played a major role in the treatment of superficial bladder cancer since the introduction of intravesical bacillus Calmette-Guérin (BCG); randomized trials have demonstrated treatment with intravesical BCG results in lower recurrence rates and significantly superior survival rates. ⁴ While the mechanism of action of BCG remains poorly defined, studies support an immunological mechanism including the role of BCG in the maturation of dendritic cells by signaling through Toll-like receptors, and secretion of inflammatory cytokines such as IL-12, IFN- γ , and TNF- α . ⁵ Increasing evidence reveals more advanced stages of bladder cancer are particularly immunogenic. Multiple studies have shown that bladder cancer specimens harbor tumor infiltrating lymphocytes ⁶⁻⁷; immunohistochemical staining for intratumoral CD8 T cells in tissue samples from 69 patients with bladder cancer (pT2, pT3, or pT4) demonstrated that patients with higher numbers of CD8 tumor infiltrating lymphocytes within the tumor (8 or more) had better disease-free survival ($P < 0.001$) and overall survival ($P = 0.018$) than did patients with similar-staged bladder cancer and fewer intratumoral CD8 tumor infiltrating lymphocytes. ⁷

Despite the immunogenicity of bladder cancer, patients with bladder cancer also exhibit tumor-associated immunologic suppression. Patients with bladder cancer exhibit a tumor-

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associated immunologic suppression, particularly evident as an impaired T-cell response, which may worsen with advanced tumor stage.⁸⁻¹⁰ Bladder cancer specimens have been shown to be infiltrated by T regulatory cells, and to express high levels of inhibitory cytokines.⁹ In addition, aberrant expression of T-cell coregulatory molecules, known to inhibit the immune response, have been demonstrated on bladder cancer cells and tumor infiltrating lymphocytes and have correlated with clinical outcomes.¹¹

These findings suggest that the balance between CD8+ cytotoxic T cells and negative immune regulatory elements in the tumor microenvironment may be critical in determining the host's overall immune response and ultimate clinical outcome.

Blocking Cytotoxic T Lymphocyte Antigen-4 (CTLA-4) may break immune tolerance in bladder cancer. Engagement of the T cell antigen receptor by itself is insufficient for full T cell activation; a second co-stimulatory signal is required. The primary source of this co-stimulation is through engagement of CD28 on the T cell surface by members of the B7 family on antigen-presenting cells. However, upon activation, T cells transiently express CTLA-4, which binds to member of the B7 family with much higher affinity than CD28, and down regulates T cell responses. Blockade of CTLA-4 has been shown to enhance T cell activation in animal models and results in an increased ratio of effector to regulatory T cells, which correlates with tumor regression.¹²⁻¹⁴ In a study of MB49 bladder cancer murine xenografts, combined antibody blockade of CTLA-4 plus local toll-like receptor stimulation with CpG resulted in a complete response rate of 86%, an increase in numbers of circulating tumor-specific CD107a expressing CD8+ T cells, and a decrease in the numbers of local T regulatory cells.¹⁵

The anti-CTLA4 antibody ipilimumab has shown safety and efficacy in patients with metastatic solid tumors and intriguing activity in localized bladder cancer. Ipilimumab is a human immunoglobulin G (IgG1) κ anti-CTLA-4 monoclonal antibody (mAb). A recent randomized phase III trial of ipilimumab plus gp100 vaccine versus ipilimumab alone versus gp100 alone demonstrated a significant improvement in survival among patients receiving ipilimumab; grade 3-4 immune-related adverse events occurred in 10-15% of patients.¹⁶ Ipilimumab has been explored pre-cystectomy in a pilot trial of patients with clinically localized bladder cancer. In this trial, 12 patients were treated with two doses of ipilimumab (6 with 3 mg/kg and 6 with 10 mg/kg).¹⁷ Most drug-related adverse events were grade 1 or 2, all patients demonstrated an increase in CD4⁺ ICOS^{hi} T cells in tumor tissue and systemic circulation, and 8/12 patients had downstaging of their disease on final pathology review. Notably, a retrospective analysis of peripheral blood samples from patients with metastatic melanoma who were treated with ipilimumab revealed that a sustained increase in peripheral blood CD4⁺ ICOS^{hi} T cells at 12 weeks correlated with improved overall survival.

Several lines of evidence suggest that the immune system can be activated by chemotherapy. Mechanisms by which chemotherapy may enhance tumor immunity include: a) eliciting cellular responses that render tumor cell death immunogenic, b) transient lymphodepletion, and c) direct or indirect stimulatory effects on immune effectors. Specifically, gemcitabine has been shown to induce apoptosis of established tumor cells in vivo, thereby increasing tumor antigen cross-presentation leading to priming of tumor-specific CD8+ T cells.¹⁸ Gemcitabine has also been shown to have selective detrimental effects on B lymphocytes inhibiting tumor-specific antibody production, which may skew antitumor immunity towards therapeutic T cell responses.¹⁹ In a

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tolerogenic tumor model in mice, gemcitabine combined with immunotherapeutic approaches resulted in potent therapeutic antitumor immunity and was shown to eliminate myeloid-derived suppressor cells.²⁰

Taken together, these data support approaches combining gemcitabine plus cisplatin with ipilimumab for the treatment of advanced bladder cancer

CTLA-4 and Ipilimumab. Advances in the understanding of the mechanisms that regulate T cell activation have allowed the rational design of new strategies for immunotherapy of tumors, including melanoma. It has been known for some time that engagement of the T cell antigen receptor by itself is not sufficient for full T cell activation; a second co-stimulatory signal is required for induction of IL-2 production, proliferation and differentiation to effector function of naive T cells. Abundant data now indicate that the primary source of this co-stimulation is mediated by engagement of CD28 on the T cell surface by members of the B7 family on the antigen-presenting cell (APC).

Expression of B7 has been shown to be limited to “professional” antigen presenting cells; that is, specialized cells of the hematopoietic lineage, including dendritic cells, activated macrophages, and activated B cells. It has been suggested that this sharply defined restriction of B7 expression is a fail-safe mechanism for maintenance of peripheral T cell tolerance, insuring that T cell activation can only be stimulated by appropriate APCs. The fact that tumor cells do not express B7 contributes to their poor capacity to elicit immune responses.

The demonstration that induction of expression of B7 on many tumor cells by transfection, transduction, or other mechanisms can heighten tumor immunogenicity led to great interest in pursuing this as an approach to tumor immunotherapy. As demonstrated in vivo in murine tumor models, the utility of B7 expression as a vaccination approach is limited by the following factors: (1) B7-expressing tumor cell vaccines are only effective when the tumor cells have a high degree of inherent immunogenicity; (2) while B7-expressing vaccines have been shown in many cases to be effective in inducing protective immune responses, they have demonstrated only limited utility in inducing responses to established tumors; and (3) inactivation of tumor cells by radiation has been shown to destroy the immuno-enhancing activity of the B7 gene product.

In the past few years, it has become apparent that co-stimulation is even more complex than originally thought. After activation, T cells express CTLA-4, a close homologue to CD28. CTLA-4 binds members of the B7 family with a much higher affinity than CD28. Although there was initially some controversy as to the role of CTLA-4 in regulating T cell activation, it has become clear that CTLA-4 down-regulates T cell responses. This was initially suggested by the following in vitro observations: (1) blockade of CTLA-4/B7 interactions with antibody enhanced T cell responses; (2) cross-linking of CTLA-4 with CD3 and CD28 inhibited T cell responses; and (3) administration of antibodies to CTLA-4 in vivo enhanced the immune response to peptide antigens or superantigens in mice. Blocking CTLA-4-B7 interaction while preserving signaling via CD28 resulted in enhanced T cell responses in vitro.

Perhaps the most convincing demonstration of the down-regulatory role of CTLA-4 came from examination of mice with a null mutation. CTLA-4 knockout mice appear to have spontaneously activated T cells evident at approximately 1 week after birth, followed by rampant

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lymphoproliferation and lymphadenopathy. These mice die at approximately 3 weeks of age, either as a result of polyclonal T cell expansion and tissue destruction or as a result of toxic shock resulting from lymphokine production by the T cells. Since thymocyte differentiation and selection proceed normally in CTLA-4-deficient mice, the rampant T cell expansion that occurs in the mice indicates that CTLA-4 plays a critical role in down-regulating T cell responses in the periphery.

Pharmacology of Ipilimumab

Ipilimumab is a human immunoglobulin G (IgG1) κ anti-CTLA-4 monoclonal antibody (mAb). In vitro studies were performed with ipilimumab to demonstrate that it is specific for CTLA-4, actively inhibits CTLA-4 interactions with B7.1 and B7.2, does not show any cross-reactivity with human B7.1, B7.2 negative cell lines, and stains the appropriate cells without non-specific cross-reactivity in normal human tissues, as demonstrated by immunohistochemistry. Ipilimumab does cross-react with CTLA-4 in non-human primates including cynomolgus monkeys.

Ipilimumab was originally produced and purified from a hybridoma clone. Subsequently, a transfectoma (CHO cell) has been generated that is capable of producing more ipilimumab on a per cell basis than the hybridoma. Material from the transfectoma will be utilized in this and future ipilimumab clinical studies. Biochemical, immunologic and in vivo preclinical primate assessments demonstrated similarity between hybridoma and transfectoma-derived ipilimumab.

Pre-Clinical Toxicology of Ipilimumab

Complete information on the pre-clinical toxicology studies can be found in the Ipilimumab Investigator Brochure (IB). Non-clinical toxicity assessments included in vitro evaluation for the potential of ipilimumab to mediate complement-dependent cellular cytotoxicity (CDCC) or antibody-dependent cellular cytotoxicity (ADCC), and toxicology assessments in cynomolgus monkeys alone and in the presence of vaccines.

The in vitro studies demonstrated that ipilimumab did not mediate CDCC of PHA- or (CD)3-activated human T cells. However, low to moderate ADCC activity was noted at concentrations up to 50 ug/mL. These data are consistent with the requirement of high levels of antigen expression on the surface of target cells for efficient ADCC or CDCC. Since ipilimumab is a human IgG1, an isotype generally capable of mediating CDCC and ADCC, the lack of these activities is likely due to a very low expression of CTLA-4 on activated T cells. Therefore, these data suggest that ipilimumab treatment would not result in depletion of activated T cells in- vivo. Indeed, no depletion of T cells or T cell subsets were noted in toxicology studies in cynomolgus monkeys.

No mortality or signs of toxicity were observed in three independent 14-day intravenous toxicology studies in cynomolgus monkeys at multiple doses up to 30 mg/kg/dose. Furthermore, ipilimumab was evaluated in sub chronic and chronic toxicology studies in cynomolgus monkeys with and without Hepatitis B (HepB) Vaccine and Melanoma Vaccine. Ipilimumab was well tolerated alone or in combination in all studies. There were no significant changes in clinical signs, body weight values, clinical pathology values or T cell activation markers. In addition, there were no significant histopathology changes in the stomach or colon.

Human Pharmacokinetics of Ipilimumab

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Pharmacokinetic (PK) profiles for ipilimumab have been analyzed. The primary objective of Protocol MDX010-015 was to determine the safety and PK profile of single and multiple doses of ipilimumab derived from a transfectoma or hybridoma cell line. Mean plasma concentrations of ipilimumab administered at doses of 3 mg/kg (hybridoma-derived drug product); 2.8 mg/kg, 5 mg/kg, 7.5 mg/kg, 10 mg/kg, 15 mg/kg, and 20 mg/kg (transfectoma-derived drug product) demonstrated approximate dose proportionality. Equimolar doses of hybridoma-derived and transfectoma-derived drug product had comparable PK profiles. The range of mean volume of distribution at steady state (Vss) across cohorts 2.8, 3, 5, 7.5, 10, 15, and 20 mg/kg, was 57.3 to 82.6 mL/kg, indicating drug distribution was mostly limited to the intravascular space. The clearance was low (range 0.11 to 0.29 mL/h/kg) and reflective of the half-life (range 297 to 414 h), which is consistent with the long terminal disposition phase of ipilimumab. There was moderate variability in the PK parameters among subjects, with CV of 11% to 48% in AUC(0-21d), 20% to 59% in CL, and 17% to 46% in Vss.

Clinical Safety with Ipilimumab

Ipilimumab has been administered to more than 13,800 subjects with different cancers in completed and ongoing clinical trials as well as a compassion use program as of 10-Mar-2014 with a dose range between 0.3 mg/kg and 20 mg/kg and in various combinations.

In general, the safety profile of ipilimumab administered as single doses of up to 20-mg/kg and multiple doses of up to 10 mg/kg every 3 weeks was characterized by adverse reactions that were mostly immune in nature. Drug-related serious adverse events (SAEs) were reported in studies of ipilimumab administered as monotherapy, as well as in combination with vaccines, cytokines, chemotherapy, or radiation therapy.

The overall summary of safety for 2901 patients treated with ipilimumab in completed or ongoing clinical trials and a subset of 658 patients treated at the 10 mg/kg dose level is presented in Table 1.

Table 1: Ipilimumab - Overall Summary of Safety

	Number of Subjects (%)	
	Ipilimumab 0.3 - 20 mg/kg N = 2901	Ipilimumab 10 mg/kg N = 658
Any Drug-related AE	2357 (81.2)	561 (85.3)
Grade 1	699 (24.1)	158 (24.0)
Grade 2	889 (30.6)	198 (30.1)
Grade 3	617 (21.3)	163 (24.8)
Grade 4	127 (4.4)	38 (5.8)
Grade 5	20 (0.7)	4 (0.6)
Any Serious Adverse Events	1258 (43.4)	310 (47.1)
Grade 3 - 4	806 (27.8)	179 (27.2)
Any Drug-related Serious Adverse Events	595 (20.5)	179 (27.2)
Grade 3 - 4	469 (16.2)	140 (21.3)

Details of Drug-Related Adverse Events

Treatment-emergent adverse events (AEs) considered by the investigator to be related to study drug were reported for 81.2% of all treated subjects and 85.3% of subjects treated with ipilimumab at 10 mg/kg. Among all treated subjects, the most frequently reported treatment-related AEs of any grade included fatigue (27.8%), diarrhea (27.5%), nausea (23.4%), rash (21.8%), pruritus (19.9%), pyrexia (11.9%), and vomiting (11.7%). Similarly, among subjects treated with ipilimumab at 10 mg/kg, the most frequently reported treatment-related AEs of any grade included diarrhea (38.1%), fatigue (30.5%), rash (34.5%), pruritus (29.8%), nausea (17.6%), pyrexia (12.3%), vomiting (10.9%), and colitis (10.2%).

Details of Drug-Related Serious Adverse Events

Among 2901 treated subjects, SAEs considered possibly, probably, or definitely related to study drug were reported for 20.5% of subjects. Drug-related SAEs reported in at least 1% of the 2901 subjects included diarrhea (5.8%), colitis (4.7%), ALT increased (2.3%), AST increased (2.2%), pyrexia (1.6%), and vomiting (1.3%). Among 658 subjects who received ipilimumab at 10 mg/kg, SAEs considered possibly, probably, or definitely related to study drug were reported for 27.2% of subjects. Drug-related SAEs reported in at least 1% of the 658 subjects treated at 10 mg/kg included diarrhea (8.5%), colitis (7.0%), vomiting (2.1%), AST increased (2.1%), ALT increased (2.0%), autoimmune hepatitis (2.0%), pyrexia (1.8%), hypopituitarism (1.7%), dehydration (1.7%), nausea (1.2%), and abdominal pain (1.1%).

Immune-Related Adverse Events (irAEs) with Ipilimumab

Many of the adverse events considered related to ipilimumab may be immune in nature and presumably a consequence of the intrinsic biological activity of ipilimumab. An irAE is defined as any adverse event associated with drug exposure and consistent with an immune-mediated event. Disease progression, infections and other etiologic causes are ruled out or deemed unlikely as contributing to the event. Supportive data, such as autoimmune serology tests or biopsies, are

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helpful but not necessary to deem an event an irAE. Events of unclear etiology, which were plausibly “immune-mediated,” have been conservatively categorized as irAEs even if serologic or histopathology data are absent. These irAEs likely reflect a loss of tolerance to some self-antigens or an unchecked immune response to gut or skin flora. Some breakthrough of immunity may be inseparably linked to the clinical antitumor activity of ipilimumab.

Immune-related AEs predominately involve the GI tract, endocrine glands, liver or skin. Among 2901 treated subjects, 59.6% (1729/2901) of subjects reported any irAE and 15.2% (441/2901) of subjects reported serious irAEs. Among subjects who received ipilimumab at 10 mg/kg, 21.9% (144/658) of subjects reported serious irAEs.

Table 2 summarizes the incidence of serious irAEs among all treated subjects and subjects who received ipilimumab 10 mg/kg.

Table 2: Serious Immune-related Adverse Events Reported for at Least 2% of Subjects in any Event Category

	Number of Subjects (%)	
	Ipilimumab 0.3 - 20 mg/kg N = 2901	Ipilimumab 10 mg/kg N = 658
irAEs ^a		
Any	441 (15.2)	144 (21.9)
Grade 3	298 (10.3)	87 (13.2)
Grade 4	59 (2.0)	25 (3.8)
GI irAE ^a		
Any	236 (8.1)	85 (12.9)
Grade 3	166 (5.7)	58 (8.8)
Grade 4	17 (0.6)	10 (1.5)
Liver irAE ^a		
Any	109 (3.8)	33 (5.0)
Grade 3	72 (2.5)	18 (2.7)
Grade 4	32 (1.1)	13 (2.0)
Endocrine irAE ^a		
Any	61 (2.1)	21 (3.2)
Grade 3	44 (1.5)	12 (1.8)
Grade 4	3 (0.1)	1 (0.2)

^aBased on treatment-related adverse events retrieved from the clinical database using pre-defined MedDRA terms that were considered potential irAEs.

With few exceptions, irAEs were clinically manageable and reversible with supportive care or corticosteroids.

Corticosteroid treatment did not adversely affect antitumor responses in those subjects who had both an irAE requiring steroid therapy and an objective tumor response. Systemic corticosteroids do not appear adversely associated with ipilimumab-induced clinical response when used to manage irAEs in patients with advanced melanoma. Similar results were observed regardless of whether modified World Health Organization (mWHO) or the novel irRC criteria were used.

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Steroids can be used promptly to manage severe irAEs and minimize the risk for serious complications. In the setting where subjects were enrolled to receive ipilimumab every 3 weeks dosing until progression, irAEs could be reported at any time, with colitis and rash reported most often during the early doses and hypophysitis reported with later doses.

Gastrointestinal irAEs

The most common Grade 3 or greater irAE involved the lower GI tract and clinically manifested as diarrhea or hematochezia. Diarrhea resulting from treatment with ipilimumab ranged from mild to severe and was life threatening in some cases. Some cases of diarrhea began as mild and became very severe. Among subjects who received ipilimumab at 10 mg/kg, GI irAEs of any grade were reported for 40.0% (263/658) of subjects, and Grade 3 - 4 GI irAEs were reported for 12.6% (83/658) of subjects. Serious GI irAEs, mostly involving diarrhea or colitis, were reported in 12.9% (85/658) of subjects treated with ipilimumab at 10 mg/kg.

Inflammatory Hepatotoxicity

Immune-related hepatic dysfunction, including hepatitis or abnormal liver function tests (LFT) attributed to ipilimumab therapy, has been reported. Subjects may develop elevations in LFTs in the absence of clinical symptoms. Inflammatory hepatotoxicity includes non-infectious hepatitis (e.g., autoimmune hepatitis). Among subjects who received ipilimumab at 10 mg/kg, inflammatory hepatotoxicity of any grade was reported for 9.0% (59/658) of subjects, and Grade 3 - 4 inflammatory hepatotoxicity was reported for 6.4% (42/658). Serious inflammatory hepatotoxicity has been reported in 5.0% (33/658) of subjects who received ipilimumab at 10 mg/kg. Inflammatory hepatotoxicity is usually reversible when immediately treated with high-dose steroids, if applicable, with or without additional immunosuppressants as recommended in the hepatotoxicity management algorithm.

Hypophysitis/Hypopituitarism and Other Endocrine Conditions

Hypophysitis/hypopituitarism, clinically manifested by fatigue, has been reported. Most subjects with hypopituitarism presented with nonspecific complaints such as fatigue, confusion, visual disturbance, or impotence. Some had headache as the predominant presentation. The majority of subjects with hypopituitarism demonstrated enlarged pituitary glands based on brain magnetic resonance imaging (MRI). Low adrenocorticotrophic hormone (ACTH) and cortisol were the most common biochemical abnormality reported; low thyroid-stimulating hormone (TSH), testosterone, or prolactin was also reported in some subjects.

Hypophysitis/hypopituitarism was controlled with appropriate hormone-replacement therapy and may be dose related. Among subjects who received ipilimumab at 10 mg/kg, endocrinopathy of any grade was reported for 7.6% (50/658) of subjects, and Grade 3-4 endocrinopathy was reported for 2.4% (16/658) of subjects. Serious drug-related endocrinopathy, such as hypophysitis/hypopituitarism, was reported in 3.2% (21/658) of subjects who received ipilimumab at 10 mg/kg.

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The first onset of endocrine irAEs typically occurred between weeks 6 and 12 of treatment. Endocrine events were generally manageable with hormone-replacement therapy, and the majority of subjects were not weaned from steroids.

Rash and Other Skin Conditions

Rash was one of the most common irAEs, and most cases were Grade 1 or 2 in intensity; pruritus has also been reported. When biopsied, pleomorphic infiltrates were noted in the skin. Among subject who received ipilimumab at 10 mg/kg, skin irAEs of any grade were reported for 52.9% (348/658) of subjects, and Grade 3 - 4 skin irAEs were reported for 2.9% (19/658) of subjects. Serious skin irAEs were reported in < 1% (4/658) of subjects who received ipilimumab at 10 mg/kg. Skin irAEs were generally reversible.

Other presumed irAEs reported include, but were not limited to, arthritis/arthralgias, pneumonitis, pancreatitis, autoimmune (aseptic) meningitis, autoimmune nephritis, pure red cell aplasia, non-infective myocarditis, ocular inflammation, Guillain-Barre syndrome (GBS), myasthenia gravis, and neuropathy (e.g., motor neuropathy, neuritis), of which were individually reported for < 1% of subjects.

Other reported irAEs

Ocular inflammation, manifested as Grade 2 or Grade 3 episcleritis or uveitis, was associated with concomitant diarrhea in a few subjects and occasionally occurred in the absence of clinically apparent GI symptomsⁱ. Serious ocular inflammation was reported in 1 of 658 (0.2%) subjects who received ipilimumab at 10 mg/kg (8 [0.3%] of 2901 subjects program-wide reported serious ocular inflammation). Preliminary analysis (based on the manual extraction of the SAE data from the internal safety database) indicated that the median time to event onset was approximately 61 days (range: 14 - 114 days). Based on the available data with known outcome, most of the subjects recovered or improved with or without corticosteroid therapy with a median duration of approximately 6 days (range: 5 - 23 days).

Drug-Related Deaths

Based on reports from the safety database as of June 30, 2009, there have been reports of death (approximately 1% [35/3800]), deemed by the investigator as possibly related to the administration of study drug. The most common cause of drug related deaths was GI perforation. Other causes included multi-organ failure, sepsis, hypotension, acidosis, and adult respiratory distress syndrome. For details on all drug-related deaths, refer to the current version of the Ipilimumab Investigator Brochure.

Safety of 10 mg/kg Multiple Doses

Based on a review of the program-wide SAE data as previously reported, evidence had suggested that ipilimumab-associated irAEs were dose dependent in frequency, and higher irAE rates had been observed at 10 mg/kg than at lower doses of ipilimumab. Subsequently, this dose-dependent effect was further demonstrated in CA184-022 in which three dose levels of ipilimumab were

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studied, including 0.3 vs 3 vs 10 mg/kg. Table 3 summarizes the overall irAE frequencies by dose from CA184-022 based on safety data from the locked clinical database.

Qualitatively, the safety profile of ipilimumab at 10 mg/kg remains consistent with the low-dose safety profile in that most of the drug-related SAEs are characteristic of immune-related toxicity, and most of the irAEs are reported in the GI, hepatic, and endocrine systems. However, the data presented in Table 3 suggest that the frequency of irAEs in association with 10 mg/kg of ipilimumab at multiple doses is higher compared with the irAE frequency reported for lower doses.

Table 3: Summary of Immune-Related Adverse Events (irAEs) by Treatment Groups - Treated Subjects (CA184-022)

	Number of Subjects (%)		
	Ipilimumab		
	0.3 mg/kg (N=72)	3 mg/kg (N=71)	10 mg/kg (N=71)
Overall irAEs	26.4	64.8	70.4
Grade 3-4	0	7.0	25.4
GI irAEs	16.7	32.4	39.4
Grade 3-4	0	2.8	15.5
Hepatic irAEs	0	0	2.8
Grade 3-4	0	0	2.8
Endocrine irAEs	0	5.6	4.2
Grade 3-4	0	2.8	1.4
Skin irAEs	12.5	45.1	46.5
Grade 3-4	0	1.4	4.2

Neuropathies

Isolated cases of motor neuropathy of an autoimmune origin have been reported among patients treated with ipilimumab. Three cases have been diagnosed as Guillain-Barre syndrome (GBS), two of which were considered study related. In both cases, the GBS was atypical in nature and more clinically resembled polyneuritis. As of 30 June 2009, 27 cases of neuropathy SAEs have been reported. Of these, 22 were assessed as unrelated to study therapy because alternative etiologies, including brain metastases, spinal cord compression, arterial thrombosis, or platinum-based chemotherapy were identified in almost every case.

Clinical Efficacy of Ipilimumab

Treatment with ipilimumab has demonstrated clinically important and durable tumor responses in several malignancies including melanoma, prostate cancer, and renal cell carcinoma. The most extensively studied tumor type has been malignant melanoma and the principal demonstration of the efficacy of ipilimumab comes from a phase III trial of ipilimumab versus placebo as second line therapy in patients with metastatic melanoma. In this trial, patients were randomized to ipilimumab plus the gp100 vaccine, ipilimumab alone, or gp100 alone. The median overall survival was 10.0 months among patients receiving ipilimumab plus gp100, as compared with 6.4

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months among patients receiving gp100 alone (hazard ratio for death, 0.68; $P < 0.001$). The median overall survival with ipilimumab alone was 10.1 months (hazard ratio for death in the comparison with gp100 alone, 0.66; $P = 0.003$). No difference in overall survival was detected between the ipilimumab groups (hazard ratio with ipilimumab plus gp100, 1.04; $P = 0.76$).¹⁶ Notably, several analyses have suggested an association between the development of irAEs and response to therapy.

Rationale for a Phase II Trial of Gemcitabine, Cisplatin, plus Ipilimumab in Urothelial Carcinoma

A study exploring the combination of gemcitabine, cisplatin, and ipilimumab in advanced urothelial carcinoma is supported by the following:

1. Gemcitabine plus cisplatin is standard treatment for advanced urothelial cancer; while the majority of patients respond to treatment, response durations are short with a median survival of 14 months.
2. Immunotherapy (with BCG) has played a major role in the treatment of non-muscle invasive urothelial carcinoma. However, immunotherapeutic approaches for advanced disease have been largely unsuccessful.
3. CTLA4 blockade with ipilimumab is a novel approach to immunotherapy involving augmentation of cell mediated immunity by interrupting T-cell pathways responsible for immune down-regulation or tolerance. Ipilimumab has shown activity in a range of advanced solid tumors and has resulted in improved survival in patients with melanoma.
4. Ipilimumab has shown intriguing activity as neoadjuvant therapy in patients with clinically localized bladder cancer undergoing radical cystectomy.
5. Several preclinical and clinical studies support additive/synergistic effects of combination chemotherapeutic and immunotherapeutic approaches. Ipilimumab has been administered in combination with chemotherapy in several clinical trials and has demonstrated safety and intriguing antitumor activity. In a phase II study, patients with chemotherapy-naïve, recurrent or stage IIIB/IV non-small cell lung cancer were randomized 1:1:1 to receive either: ipilimumab (10 mg/kg IV q3wks) + concurrent paclitaxel/carboplatin, ipilimumab + sequential paclitaxel + carboplatin, or paclitaxel plus carboplatin alone.²¹ There were generally manageable and reversible immune related adverse events and rare and comparable drug related deaths across all study arms. There was an improvement in progression-free survival with the addition of ipilimumab.
6. Combination gemcitabine, cisplatin, plus ipilimumab may build on the chemosensitivity of urothelial carcinoma to produce more durable responses and improved outcomes.

Rationale for using immune-related Tumor Assessment Criteria (irRC)

Ipilimumab is an immune-stimulating antibody with evidence of anti-cancer activity (durable objective response and stable disease) across various solid tumors. Observations of clinical activity defined by tumor response endpoints defined by conventional criteria (e.g., mWHO) may be inadequate to realize the kinetics and magnitude of clinical benefit achieved with ipilimumab.

Histopathological evidence has demonstrated ipilimumab can produce an influx or expansion of tumor infiltrating lymphocytes. Therefore, early increases in lesion size detected radiologically or

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upon gross examination could be misinterpreted as progressive tumor growth and precede objective tumor shrinkage. In addition the appearance of new lesions may have categorized a subject to have progressive disease using conventional tumor assessment criteria despite the concurrent observation of objective tumor responses in preexisting lesions and a net reduction in global tumor burden that includes the new lesions.

Hence, the appearance of new lesions in and of themselves may not necessarily constitute progressive disease. The immune-related response criteria (irRC) were developed as a tool to gauge tumor response using the changes in global tumor burden²². In addition, the irRC may be useful to inform a physician's decision to continue dosing in subjects who may receive benefit from additional ipilimumab therapy. The ir-response assessment is based solely on objective measurements (sum of the product of the 2 largest perpendicular diameters, SPD) of index and new lesions. Non-index lesions are not considered. The irRC identified 9.7% of subjects (22/227 treated subjects) from CA184022 and CA184008 at 10 mg/kg who demonstrated disease control in the form of stable or reduced measurable tumor burden, including new lesions, at or after disease progression by mWHO.

For the current trial, response will be assessed both by irRC and RECIST v1.0 providing additional data for comparisons of these systems of response assessment in patients receiving combination immune plus cytotoxic therapy.

2.0 OBJECTIVES

2.1 Primary Objective:

- To determine the 1-year overall survival of patients with advanced/metastatic urothelial carcinoma treated with gemcitabine, cisplatin, plus ipilimumab.

2.2 Secondary Objectives:

- To determine the progression-free survival (using irRC) of patients with advanced/metastatic urothelial carcinoma treated with gemcitabine, cisplatin, and ipilimumab.
- To determine the disease control rate (complete response + partial response + stable disease using irRC and RECIST v1.0 [see Section 8.2]) to treatment with gemcitabine, cisplatin, plus ipilimumab.
- To determine the safety of treatment with gemcitabine, cisplatin, plus ipilimumab.

2.3 Exploratory Objectives:

- To serially monitor the global composition immune cells in the blood by polychromatic flow cytometry and correlate changes with clinical outcome.
- To determine the frequency of tumor-antigen specific CD8+ T cells by antigen-specific multi-cytokine production (IFN- γ , TNF- α and IL-2) by intracellular cytokine staining.
- To perform transcriptional profiling of blood samples before and after treatment using microarray and correlate changes with clinical outcomes.

3.0 ELIGIBILITY CRITERIA

- 3.1** Written informed consent and HIPAA authorization for release of personal health information.

NOTE: HIPAA authorization may be included in the informed consent or obtained separately.

- 3.2** Age ≥ 18 years at the time of consent.
- 3.3** Karnofsky performance status (KPS) $\geq 80\%$ within 7 days prior to registration for protocol therapy.
- 3.4** Women of childbearing potential (WOCBP) must be using an adequate method of contraception to avoid pregnancy throughout the study and for up to 26 weeks after the last dose of investigational product, in such a manner that the risk of pregnancy is minimized.

WOCBP include any female who has experienced menarche and who has not undergone successful surgical sterilization (hysterectomy, bilateral tubal ligation, or bilateral oophorectomy) or is not post-menopausal. Post-menopause is defined as: Amenorrhea ≥ 12 consecutive months without another cause, or for women with irregular menstrual periods and taking hormone replacement therapy (HRT), a documented serum follicle-stimulating hormone (FSH) level ≥ 35 mIU/mL.

Women who are using oral contraceptives, other hormonal contraceptives (vaginal products, skin patches, or implanted or injectable products), or mechanical products such as an intrauterine device or barrier methods (diaphragm, condoms, spermicides) to prevent pregnancy, or are practicing abstinence or where their partner is sterile (e.g., vasectomy) should be considered to be of childbearing potential.

- 3.5** WOCBP must have a negative serum or urine pregnancy test (minimum sensitivity 25 IU/L or equivalent units of HCG) within 72 hours before the start of ipilimumab.
- 3.6** Men of fathering potential must be using an adequate method of contraception to avoid conception throughout the study [and for up to 26 weeks after the last dose of investigational product] in such a manner that the risk of pregnancy is minimized.
- 3.7** Females must not be pregnant or breastfeeding.
- 3.8** Histological or cytological proof of urothelial carcinoma of the urethra, bladder, ureters, or renal pelvis.
- 3.9** Advanced (clinical stage T4b, unresectable) or metastatic disease.

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- 3.10** No active CNS metastases. Subjects with neurological symptoms must undergo a head CT scan or brain MRI to exclude brain metastasis within 28 days of registration.

NOTE: A subject with prior brain metastasis may be considered if they have completed their treatment for brain metastasis, no longer require corticosteroids, and are asymptomatic.

- 3.11** No prior malignancy is allowed except for cancers that have been definitively treated with a risk of recurrence of < 30% based on the treating oncologist's assessment.

- 3.12** Patients may not have received prior systemic chemotherapy for metastatic/advanced urothelial carcinoma.

NOTE: Prior neoadjuvant/adjuvant therapy is permitted if completed ≥ 12 months prior to registration for protocol therapy. Prior intravesical therapy is permitted.

- 3.13** No treatment with any investigational agent within 30 days prior to registration for protocol therapy.

- 3.14** Prior radiation therapy is allowed to < 25% of the bone marrow [see bone marrow radiation chart in the study procedure manual (SPM)].

NOTE: No radiation therapy within 30 days prior to registration for protocol therapy.

- 3.15** Prior Autoimmune disease: Patients with a history of inflammatory bowel disease, including ulcerative colitis and Crohn's Disease, are excluded from this study, as are patients with a history of symptomatic disease (e.g., rheumatoid arthritis, systemic progressive sclerosis [scleroderma], systemic lupus erythematosus, autoimmune vasculitis [e.g., Wegener's granulomatosis]); motor neuropathy considered of autoimmune origin (e.g. Guillain-Barre Syndrome and Myasthenia Gravis).

NOTE: Patients with other immune disorders should not be enrolled without discussion with the principal investigator.

- 3.16** No underlying medical or psychiatric condition, which in the opinion of the investigator will make the administration of ipilimumab hazardous or obscure the interpretation of AEs, such as a condition associated with frequent diarrhea.

- 3.17** No non-oncology vaccine therapy used for prevention of infectious diseases (for up to 1 month before or after any dose of ipilimumab).

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- 3.18** No history of prior treatment with ipilimumab or prior CD137 agonist or CTLA-4 inhibitor or agonist.
- 3.19** No known active or chronic infection with HIV, Hepatitis B, or Hepatitis C.
- 3.20** No clinically significant infections as judged by the treating investigator.
- 3.21** No chronic systemic corticosteroids (defined as the equivalent of prednisone ≥ 20 mg PO daily for > 6 months during the past year)

NOTE: Laboratory values must be obtained within 7 days prior to registration for protocol therapy.

- 3.22** White blood cell count (WBC) $\geq 3.5\text{K}/\text{mm}^3$
- 3.23** Hemoglobin (Hgb) ≥ 9 g/dL
- 3.24** Platelets $\geq 100\text{K}/\text{mm}^3$
- 3.25** Absolute neutrophil count (ANC) $\geq 1.5\text{K}/\text{mm}^3$
- 3.26** Actual or Calculated creatinine clearance of ≥ 55 cc/min using the Cockcroft-Gault formula:

Males:
$$\frac{(140 - \text{Age in years}) \times \text{Actual Body Weight in kg}}{72 \times \text{Serum Creatinine (mg/dL)}}$$

Females: Estimated creatinine clearance for males $\times 0.85$
- 3.27** Bilirubin ≤ 1.5 times (\times) Upper Limit of Normal (ULN) (except patients with Gilbert's Syndrome, who must have a total bilirubin less than 3.0 mg/dL)
- 3.28** Aspartate aminotransferase (AST) $\leq 2.5 \times \text{ULN}$. **NOTE:** If the patient has liver metastases present, then $\leq 5 \times \text{ULN}$
- 3.29** Alanine aminotransferase (ALT) $\leq 2.5 \times \text{ULN}$. **NOTE:** If the patient has liver metastases present, then $\leq 5 \times \text{ULN}$
- 3.30** Patient must consent to mandatory correlative sample collection.

4.0 PATIENT REGISTRATION

All patients must be registered through the Hoosier Cancer Research Network electronic data capture (EDC) system.

Detailed guidelines for patient registration and electronic case report form (eCRF) completion can be found in the Study Procedures Manual (SPM).

Patients must be registered prior to starting protocol therapy and begin therapy within 5 working days of registration.

Blinding

The study treatment is not blinded to the patient or the investigator.

5.0 TREATMENT PLAN

Treatment during the “induction” phase will be administered in six 21-day cycles. During cycles 1 and 2, gemcitabine plus cisplatin will be administered WITHOUT ipilimumab. During cycles 3-6, combination therapy with gemcitabine, cisplatin, plus ipilimumab will be administered. Patients without evidence of disease progression (by irRC) after completion cycle 6 will continue single-agent ipilimumab “maintenance” every 3 months.

5.1 Induction:

Patients will undergo a restaging CT scan after cycle 2 and after cycle 6. However, patients with evidence of disease progression (in the absence of significant functional/symptomatic deterioration) on the post-cycle 2 CT scan will not be required to come off study as they will have not yet started ipilimumab. Patients may elect to come off study at any time.

Furthermore, as durable disease stabilization and/or objective tumor response can be seen in other advanced solid tumors after early progression before 12 weeks of ipilimumab treatment, it is recommended that, in the absence of treatment-limiting toxicities (e.g., serious irAEs), all four doses of ipilimumab be administered over the initial 12 weeks even in the setting of apparent progression, providing the subject’s performance status remains stable.

Based on clinical experience in ongoing and completed melanoma studies, the following recommendations apply for subject management in light of the post-cycle 6 or later tumor assessments:

- The appearance of new lesions in subjects with other stable or shrinking baseline tumor burden may be experiencing clinical benefit and should continue in follow-up and/or maintenance therapy before alternative anti-cancer agents are considered. These subjects can be seen to have continued tumor shrinkage in follow-up scans.
- As long as overall tumor burden is stable or decreasing, subjects should remain in follow-up and/or maintenance, even in the presence of new lesions.
- Clinical progression warranting alternative anti-cancer treatment should be considered only in subjects whose overall tumor burden appears to be substantially increased and/or in subjects whose performance status is decreased.

The irRC will be utilized which requires a confirmatory scan documenting progression²². The definition of confirmation of progression represents an increase in tumor burden $\geq 25\%$ compared with nadir at two consecutive time points at least 4 weeks apart. Therefore, patients with disease

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progression on the post-cycle 6 scan (in the absence of symptomatic/functional deterioration) should have a confirmatory CT scan at least 4 weeks later.

5.2 Maintenance:

As per the schedule of dosing in the ongoing and completed clinical studies using ipilimumab in subjects with pretreated advanced melanoma, maintenance therapy should be offered to all subjects who have not experienced unacceptable toxicity (refractory Grade > 3 irAEs) and are considered by the investigator to be obtaining clinical benefit, either because of apparent tumor stability or continued shrinkage and/or late response.

A single dose of 10 mg/kg ipilimumab given intravenously over 90 minutes should be administered every 12 weeks, starting from approximately week 28 until the subject is no longer clinically benefiting from therapy, per the investigator, or until the occurrence of unacceptable or unmanageable toxicity.

Subjects in maintenance should receive radiographic tumor assessments every 12 weeks before administration. Subjects who continue to experience clinical benefit, as defined by the investigator, and who have not experienced unacceptable toxicity (refractory Grade > 3 irAEs), are eligible to receive continued maintenance.

5.3 Pre-medication:

Gemcitabine

There are no required/recommended premedications for the administration of gemcitabine. Antiemetics may be administered per institutional guidelines.

Cisplatin

The antiemetic regimen is at the discretion of the treating physician and according to institutional standards.

Ipilimumab

There are no required premedications for the administration of ipilimumab.

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5.4 Drug Administration:**Cycles 1 and 2: Gemcitabine plus cisplatin**

Agent	Route	Dose	Administration	Frequency * (± 3 days)	Cycle Length	# Cycles
Gemcitabine	IV	1000 mg/m ²	Over 30 minutes according to institutional guidelines	Day 1, 8	21 days	1-2
Cisplatin	IV	70 mg/m ²	As per institutional guidelines	Day 1		

Cycles 3-6: Gemcitabine, Cisplatin, plus Ipilimumab

Agent	Route	Dose	Administration	Frequency * (± 3 days)	Cycle Length	# Cycles
Ipilimumab	IV	10 mg/kg	Over 90 minutes	Day 1	21 days	3-6
Gemcitabine	IV	1000 mg/m ²	Over 30 minutes according to institutional guidelines	Day 1, 8		
Cisplatin	IV	70 mg/m ²	As per institutional guidelines	Day 1		

Maintenance Single Agent Ipilimumab (starting ~ week 28)

Agent	Route	Dose	Administration	Frequency * (± 3 days)	Cycle Length	# Cycles
Ipilimumab	IV	10 mg/kg	Over 90 minutes	Day 1	3 months	Until progression

Note: * Infusions may be given ±3 days for reasons such as observed holidays, inclement weather, scheduling conflicts, etc. It should be clearly documented in patient's chart and case report forms.

Only if patient's weight changes by > 10% during the course of the study, the body surface area and chemotherapy drug dose should be recalculated. Ipilimumab dosing should be calculated at each visit using patient's current weight (obtained within 3 days of the dosing visit, and prior to the infusion).

5.5 Supportive Care:

The use of supportive care will be permitted as clinically indicated and according to institutional guidelines. The use of white blood cell and red blood cell growth factors should be consistent with American Society of Clinical Oncology (ASCO) guidelines.

5.6 Concomitant Medications:

Patients in this study may not use vaccines for the treatment of cancer or prevention of disease unless indicated as a component of the protocol regimen (including those for common medical conditions) for up to one month pre and post dosing with ipilimumab.

Concomitant systemic or local anti-cancer medications or treatments are prohibited in this study while receiving ipilimumab treatments unless as otherwise specified in this protocol.

Patients may not use any of the following therapies during the study:

- Any non-study anti-cancer agent (investigational or non-investigational)
- Any other investigational agents
- Any other (non-CA184024 related) CTLA-4 inhibitors or agonists
- CD137 agonists
- Immunosuppressive agents
- Chronic systemic corticosteroids (defined as the equivalent of prednisone ≥ 20 mg daily)
- Any non-oncology vaccine therapies used for the prevention of infectious diseases (for up to 30 days prior to or after any dose of study drug).

6.0 DOSE MODIFICATIONS

The NCI Common Terminology Criteria for Adverse Events (CTCAE) Version 4.0 will be used to grade adverse events.

Patients enrolled in this study will be evaluated clinically and with standard laboratory tests before and at regular intervals during their participation in this study as specified in Section 7.0

Patients will be evaluated for adverse events (all grades), serious adverse events, and adverse events requiring study drug interruption or discontinuation at each study visit for the duration of their participation in the study.

Patients discontinued from the treatment phase of the study for any reason will be evaluated at least 30 days after the last dose of study drug.

Dose modifications will be based on blood counts within 3 days prior to Day 1 or Day 8 of each cycle.

Each treatment cycle will begin only when:

- ANC $\geq 1.5\text{K/mm}^3$
- Platelets $\geq 100\text{K/mm}^3$

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- Resolution of non-hematologic toxicities to \leq Grade 1 or baseline
- For treatment cycles involving ipilimumab, LFT results must be reviewed by the treating physician to meet dosing criteria specifications: $\leq 2.5 \times \text{ULN}$ for AST, ALT and $\leq 1.5 \times \text{ULN}$ for T. bilirubin unless liver metastases are present in which case LFT $\leq 5 \times \text{ULN}$ for AST, ALT and T. bilirubin $\leq 3.0 \times \text{ULN}$ prior to dosing.

Patients requiring treatment to be held for toxicity > 21 days will be removed from study treatment.

6.1 Treatment Limiting Adverse Event:

A treatment-limiting adverse event is any adverse event related to protocol therapy experienced during the study resulting in treatment termination.

6.2 Dose Modifications for Treatment Related Hematological Toxicity:

Dose modifications for Day 1 Treatment (Cycle 2 through Cycle 6)

The following dose modifications will be based on blood counts within 3 days prior to **Day 1** of each cycle of therapy.

ANC		Platelets	Cisplatin dose	Lowest gemcitabine dose in prior cycle	Day 1 dose of gemcitabine
$\geq 1.5\text{K/mm}^3$	And	$\geq 100 \text{ K/mm}^3$	Continue dose of cisplatin from prior cycle (e.g., if no prior dose reductions, continue at 70 mg/m^2)	1000 mg/m^2	1000 mg/m^2
$\geq 1.5\text{K/mm}^3$	And	$\geq 100 \text{ K/mm}^3$		800 mg/m^2	800 mg/m^2
$\geq 1.5\text{K/mm}^3$	And	$\geq 100 \text{ K/mm}^3$		600 mg/m^2	600 mg/m^2
$< 1.5\text{K/mm}^3$	Or	$< 100 \text{ K/mm}^3$	*Hold and recheck in 1 week	Any	*Hold and recheck in 1 week
*Once ANC ≥ 1500 and platelets $\geq 100,000$, resume therapy with gemcitabine reduced by 1 dose level. If gemcitabine has already been reduced by 1 dose level, discuss dose reduction with principal investigator. Granulocyte colony stimulating factors may be used at the discretion of the treating physician; however, growth factors should be not used during cycle #1 or in lieu of recommended dose reductions. Treatment with ipilimumab will also be HELD until patients meet criteria to resume dosing with gemcitabine and cisplatin.					

Dose modifications for Day 8 Treatment (any cycle)

The following dose modifications of gemcitabine will be based on blood counts within 3 days prior to day 8 of each cycle of therapy.

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ANC		Platelets	if Day 1 dose level of gemcitabine was:	then Day 8 dose level of gemcitabine will be:
$\geq 1.5\text{K/mm}^3$	And	$\geq 100\text{ K/mm}^3$	1000 mg/m ²	1000 mg/m ²
$\geq 1.5\text{K/mm}^3$	And	$\geq 100,000$	800 mg/m ²	800 mg/m ²
$\geq 1.5\text{K/mm}^3$	And	$\geq 100\text{ K/mm}^3$	600 mg/m ²	600 mg/m ²
1.0K/mm ³ - 1.4 K/mm ³	And	$\geq 100\text{ K/mm}^3$	1000 mg/m ²	800 mg/m ²
<1.0 K/mm ³	Or	<100,000 K/mm ³	Any	Hold and recheck in 1 week*
*Treatment held on Day 8 should not be made up at a later date; resume next cycle as scheduled with gemcitabine reduced by 1 dose level.				

There should be no dose re-escalation after a dose reduction.

Febrile neutropenia

If febrile neutropenia develops in a given cycle, hold gemcitabine, cisplatin, and ipilimumab during febrile neutropenia.

NOTE: Doses missed on Days 8 of therapy will not be made up.

Resume gemcitabine and cisplatin at one dose lower than the dose administered in the last cycle. This dose should be used for all subsequent cycles. The dose of ipilimumab will be unchanged. Granulocyte colony stimulating factors may be used at the discretion of the treating physician.

6.3 Dose Modifications for Other Treatment Related Non-Hematological Toxicity Secondary to Gemcitabine or Cisplatin:

Dose reductions for nonhematologic toxicities attributable to gemcitabine or cisplatin (with the exception of alopecia or nausea/vomiting not optimally managed with antiemetics) are outlined in the table below. Only the drugs felt to be contributing to the toxicity per the Treating Physician should be dose reduced. Patients with treatment-related nausea that is grade ≥ 2 despite optimal use of antiemetics will be dose reduced by 1 level.

If nonhematologic toxicity occurs mid-cycle, and is attributed to gemcitabine, the Day 8 gemcitabine dose should be held and resumed with the subsequent cycle as scheduled.

Dose reductions for nonhematologic toxicities	
Nonhematologic toxicity	Gemcitabine/Cisplatin
Grade 0-2	No change
Grade 3	Hold until Grade ≤ 1 and

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	resume treatment reduced by 1 dose level
Grade 4	Hold until Grade ≤ 1 and resume treatment reduced by 1 dose level

Dose modifications for gemcitabine and cisplatin		
Dose level	Gemcitabine	Cisplatin
Dose level -1	800 mg/m ²	60 mg/m ²
Dose level -2	600 mg/m ²	50 mg/m ²

Dose re-escalation after a dose reduction for nonhematologic toxicity should not occur without discussion with the Study Investigator.

If toxicity is specifically attributable to cisplatin and warrants discontinuation of cisplatin, patients may be considered for continuation on treatment with gemcitabine and ipilimumab but this must be discussed with the Study Investigator.

6.4 Dose Modifications for Ipilimumab:

Dose de-escalation of ipilimumab from 10 mg/kg is not allowed.

Ipilimumab Dose Skipping Rule

Decisions to skip an ipilimumab dose must be made on specified safety criteria. Treatment with ipilimumab will be skipped or discontinued if the subject experiences at least one adverse event, specified below, considered by the investigator to be “possibly”, probably” or “certainly” related to ipilimumab treatment.

The following criteria will be used to determine dose skipping, restarting doses, or discontinuing ipilimumab.

It may be necessary to skip study drug dosing for the following related adverse event(s) at investigator’s discretion:

- Any \geq Grade 2 non-skin related adverse event (including irAEs), except for laboratory abnormalities
- Any \geq Grade 3 laboratory abnormality
- Any adverse event, laboratory abnormality or intercurrent illness that, in the judgment of the investigator, presents a substantial clinical risk to the subject with continued dosing.

It is necessary to skip study drug dosing for the following adverse events:

- Any \geq Grade 3 skin related adverse event regardless of causality.
- Any toxicities resulting in chemotherapy being held (unless otherwise approved by the principal investigator).

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Restart ipilimumab dosing if/when the adverse event(s) resolve(s) to \leq Grade 1 severity or returns to baseline within 2 weeks of initial dose administration:

- If the *adverse event has resolved*, restart ipilimumab dosing at the next scheduled time point per protocol.
- If the adverse event has not resolved in the protocol-specified dosing window (3 weeks, the next scheduled dose will be skipped and dosing will be resumed at the subsequently scheduled dose.
- If > 1 dose is expected to be skipped, the dosing schedule modifications must be discussed with the principal investigator prior to implementation.

The following treatment related non-neurological adverse events require permanent discontinuation of ipilimumab:

- Any \geq Grade 2 eye pain or reduction of visual acuity that does not respond to topical therapy and does not improve to \leq Grade 1 severity within 2 weeks of starting therapy, OR, requires systemic treatment.
- Any \geq Grade 3 bronchospasm or other hypersensitivity reaction.
- Any other \geq Grade 3 non-skin related adverse event with the exception of events listed under “No Discontinuation” (below).
- Any \geq Grade 4 laboratory abnormalities, except AST, ALT, or Total Bilirubin
- AST or ALT $> 8 \times$ ULN
- Total Bilirubin $> 5 \times$ ULN
- Any other \geq Grade 4 adverse event
- Any adverse event, laboratory abnormality or intercurrent illness which, in the judgment of the investigator, presents a substantial clinical risk to the patient with continued dosing.

The following neurological adverse event requires permanent discontinuation of ipilimumab and defines unacceptable neurotoxicity:

- Any motor neurologic toxicity \geq Grade 3 regardless of causality
- Any \geq Grade 3 treatment related sensory neurologic toxicity

Exceptions to Permanent Discontinuation

- Potentially reversible inflammation ($<$ Grade 4), attributable to a local anti-tumor reaction and a potential therapeutic response. This includes inflammatory reactions at sites of tumor resections or in draining lymph nodes, or at sites suspicious for, but not diagnostic of metastasis.
- Hospitalization for \leq Grade 2 adverse events where the primary reason for hospitalization is to expedite the clinical work-up.
- Patients with the following conditions where in the investigator’s opinion continuing study drug administration is justified:
 - Ocular toxicity that has responded to topical therapy.
 - Endocrinopathies where clinical symptoms are controlled with appropriate hormone replacement therapy. **Note:** Ipilimumab may not be restarted while the patient is being treated with systemic corticosteroids except for patients on stable doses of hormone replacement therapy such as hydrocortisone.

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6.5 Immune-Related Adverse Events (irAEs): Definition, Monitoring, and Treatment:

Blocking CTLA-4 function may permit the emergence of auto-reactive T cells and resultant clinical autoimmunity. Rash/vitiligo, diarrhea/colitis, uveitis/episcleritis, hepatitis, and hypopituitarism were drug-related, presumptive autoimmune events, now termed irAEs, noted in previous ipilimumab studies.

For the purposes of this study, an irAE is defined as an AE of unknown etiology associated with drug exposure and consistent with an immune phenomenon. Efforts should be made to rule out neoplastic, infectious, metabolic, toxin or other etiologic causes prior to labeling an AE an irAE. Serological, immunological, and histological (biopsy) data should be used to support the diagnosis of an immune-mediated toxicity. Suspected irAEs must be documented on an AE or SAE form.

Patients should be informed of and carefully monitored for evidence of clinically significant systemic irAE (e.g., systemic lupus erythematosus-like diseases) or organ-specific irAE (e.g., rash, colitis, uveitis, hepatitis or thyroid disease). If an irAE is noted, appropriate work-up (including biopsy if possible) should be performed, and steroid therapy may be considered if clinically necessary. .

It is unknown if systemic corticosteroid therapy has an attenuating effect on ipilimumab activity. However, clinical anti-tumor responses have been maintained in patients treated with corticosteroids and discontinued from ipilimumab. If utilized, corticosteroid therapy should be individualized for each patient. Prior experience suggests that colitis manifested as \geq Grade 3 diarrhea requires corticosteroid treatment.

Specific treatment algorithms for immune-related adverse events are included in Appendix A.

6.6 Treatment of Infusions Reactions and Fever Associated with Ipilimumab:

Treatment of Infusion Reactions Associated with Ipilimumab

Since ipilimumab contains only human protein sequences, it is less likely that any allergic reaction will be seen in patients. However, it is possible that infusion of ipilimumab will induce a cytokine release syndrome that could be evidenced by fever, chills, rigors, rash, pruritus, hypotension, hypertension, bronchospasm, or other symptoms. No prophylactic pre-medication will be given unless indicated by previous experience in an individual patient. Reactions should be treated based upon the following recommendations.

For mild symptoms (e.g., localized cutaneous reactions such as mild pruritus, flushing, rash):

- Decrease the rate of infusion until recovery from symptoms, remain at bedside and monitor patient.
- Complete the ipilimumab infusion at the initial planned rate.
- Diphenhydramine 50 mg IV may be administered at the discretion of the treating physician and patients may receive additional doses with close monitoring.

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- Premedication with diphenhydramine may be given at the discretion of the investigator for subsequent doses of ipilimumab.

For moderate symptoms (any symptom not listed above [mild symptoms] or below [severe symptoms] such as generalized pruritus, flushing, rash, dyspnea, hypotension with systolic BP >80 mmHg):

- Interrupt ipilimumab.
- Administer diphenhydramine 50 mg IV.
- Monitor patient closely until resolution of symptoms.
- Corticosteroids may abrogate any beneficial immunologic effect, but may be administered at the discretion of the treating physician.
- Resume ipilimumab infusion after recovery of symptoms.
- At the discretion of the treating physician, ipilimumab infusion may be resumed at *one half the initial infusion rate, then increased incrementally to the initial infusion rate.*
- If symptoms develop after resumption of the infusion, the infusion should be discontinued and no additional ipilimumab should be administered that day.
- The next dose of ipilimumab will be administered at its next scheduled time and may be given with pre-medication (diphenhydramine and acetaminophen) and careful monitoring, following the same treatment guidelines outlined above.
- At the discretion of the treating physician additional oral or IV antihistamine may be administered prior to dosing with ipilimumab.

For severe symptoms (e.g., any reaction such as bronchospasm, generalized urticaria, systolic blood pressure <80 mm Hg, or angioedema):

- Immediately discontinue infusion of ipilimumab, and disconnect infusion tubing from the subject.
- Consider bronchodilators, epinephrine 1 mg IV or subcutaneously, and/or diphenhydramine 50 mg IV, with Solu-Medrol 100 mg IV, as needed.
- Patients should be monitored until the investigator is comfortable that the symptoms will not recur.
- No further ipilimumab will be administered.

In case of late-occurring hypersensitivity symptoms (e.g., appearance within one week after treatment of a localized or generalized pruritus), symptomatic treatment may be given (e.g., oral antihistamine, or corticosteroids).

Treatment of Ipilimumab-Related Isolated Drug Fever

In the event of isolated drug fever, the investigator must use clinical judgment to determine if the fever is related to the ipilimumab or to an infectious etiology. If a patient experiences isolated drug fever, for the next dose, pre-treatment with acetaminophen or non-steroidal anti-inflammatory agent (investigator discretion) should be instituted and a repeated antipyretic dose at 6 and 12 hours after ipilimumab infusion should be administered. The infusion rate will remain unchanged for future doses. If a patient experiences recurrent isolated drug fever following premedication and post dosing with an appropriate antipyretic, the infusion rate for subsequent dosing should be decreased to 50% of the

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previous rate. If fever recurs following infusion rate change, the investigator should assess the patient's level of discomfort with the event and use clinical judgment to determine if the patient should receive further ipilimumab.

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7.0 STUDY CALENDAR & SCHEDULE OF EVALUATIONS**Induction****Maintenance Ipilimumab**

	Pre-study		Cycle 1-2 ¹ (cycle = 21 days)		Cycles 3-6 ¹ (cycle = 21 days)		Cycle Length = 3 months			End of Treatment	Follow-up
	-28 days	-7 days	Day 1	Day 8	Day 1	Day 8	Day 1	Day 30 ± 7	Day 60 ± 7	(30 ± 7 days post last treatment)	Follow-up ¹⁰
REQUIRED ASSESSMENTS											
Medical & smoking history		X									
Height		X									
Physical examination		X	X	X ²	X	X ²	X	X	X	X	
Blood pressure		X	X	X	X	X	X	X	X	X	
Weight [Kg]		X	X	X	X	X	X	X	X	X	
KPS		X	X	X	X	X	X	X	X	X	
ECG		X									
CMP ³		X	X		X ⁴		X ⁴	X	X	X	
TSH ⁵					X		X				
Calculated creatinine clearance		X									
CBC (including platelets, ANC & Hgb)		X	X	X	X	X	X	X	X	X	
Urine pregnancy		X			X ⁶						
Adverse event and concomitant medication assessment		X	X	X	X	X	X	X	X	X	
DISEASE ASSESSMENT											
CT chest , abdomen, pelvis ⁷	X		Disease evaluations will be performed after cycle 2 and after cycle 6				Disease evaluations will be performed prior to each maintenance cycle			X ⁹	X
Bone Scan (if clinically indicated) ⁸	X									X ⁹	X
TREATMENT											
Gemcitabine			X	X	X	X					
Cisplatin			X		X						
Ipilimumab					X		X				
CORRELATIVE STUDIES											
Mandatory blood draws. See Section 7, Table 4											
Unstained tissue slides ¹¹			X								
FOLLOW-UP											
Disease progression and survival											X

Calendar Footnotes on next page.

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1. There will be a window of ± 3 days for the start of each cycle, and a window of ± 3 day for each Day 8 visit.
2. Abbreviated physical examination targeted to signs and symptoms
3. Complete metabolic profile (CMP) will include: serum chemistries (creatinine, glucose, total protein, blood urea nitrogen [BUN], total carbon dioxide [CO_2], albumin, total bilirubin, alkaline phosphatase, and aspartate transaminase [AST] and alanine transaminase [ALT]) and electrolytes (total calcium, chloride, potassium, sodium).
4. Liver function tests (AST, ALT, T. bilirubin) will be evaluated for every subject prior to administration of ipilimumab. Blood samples must be collected and analyzed within 3 days prior to dosing. LFT results must be reviewed by the treating physician to meet dosing criteria specifications: $\leq 2.5 \times \text{ULN}$ for AST, ALT and $\leq 1.5 \times \text{ULN}$ for T. bilirubin unless liver metastases are present in which case $\text{LFT} \leq 5 \times \text{ULN}$ for AST, ALT and T. bilirubin $\leq 3.0 \times \text{ULN}$ prior to dosing. If, during the course of treatment abnormal LFT values are detected, the subject must be managed using the hepatotoxicity algorithm, which is included as an Appendix.
5. Results are needed prior to Ipilimumab dosing.
6. WOCBP must have a negative serum or urine pregnancy test (minimum sensitivity 25 IU/L or equivalent units of HCG) within 72 hours before the start of ipilimumab.
7. Patients will continue therapy, in the absence of prohibitive toxicities, until disease progression. Patients discontinuing treatment for reasons other than progression will be followed for disease progression and survival every 3 months (± 7 days) for 2 years, every 6 months (± 7 days) for years 3 - 5, and annually thereafter.
8. Bone scan only if clinically indicated (elevated alkaline phosphatase, bone pain)
9. A repeat CT scan is not required at end of treatment if performed within the 28 days.
10. All patients who receive study drug will be followed for disease progression and survival every 3 months (± 7 days) for 2 years from completion of protocol therapy, every 6 months (± 7 days) for years 3 - 5, and annually thereafter.
11. Unstained slides from the patients previously collected tumor tissue are to be submitted. Please refer to the Study Procedures Manual for collection and shipping instructions.

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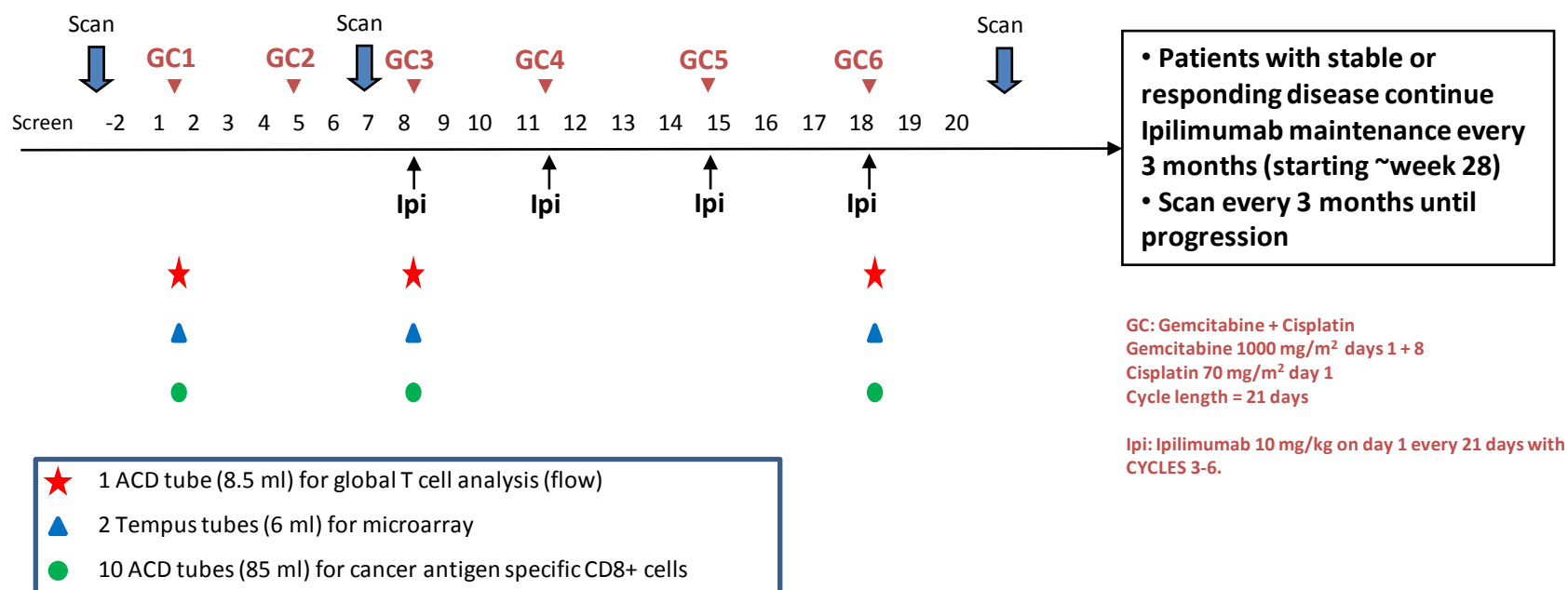
Figure and Table 4: Schedule for correlative blood sample collections (refer to study procedure manual for specimen processing and shipping instruction)

Table 4: Schedule for correlative blood sample collections

Time point	Correlative blood samples
Cycle 1 Day 1	1 ACD tube (8.5 ml total) 2 Tempus tubes (6 ml total) 10 ACD tubes (85 ml total)
Cycle 3 Day 1	1 ACD tube (8.5 ml total) 2 Tempus tubes (6 ml total) 10 ACD tubes (85 ml total)
Cycle 6 Day 1	1 ACD tube (8.5 ml total) 2 Tempus tubes (6 ml total) 10 ACD tubes (85 ml total)
Maintenance Cycle 1 Day 1	1 ACD tube (8.5 ml total) 2 Tempus tubes (6 ml total)
Time of progression	1 ACD tube (8.5 ml total) 2 Tempus tubes (6 ml total)

7.1 BASELINE/SCREENING**7.1.1 Within 28 days prior to registration for protocol therapy:**

- Radiological assessment (CT chest, abdomen, and pelvis) with tumor measurements; and
- Bone Scan if clinically indicated (e.g., elevated alkaline phosphatase, bone pain)

7.1.2 Within 7 days of registration for protocol therapy:

- Eligibility evaluation (review of inclusion criteria)
- Medical & smoking history
- Height
- Blood pressure
- Weight [kg]
- Concomitant medications
- Physical examination
- Karnofsky Performance Status (KPS)
- 12-lead electrocardiogram (ECG)
- Complete metabolic profile (CMP) will include: serum chemistries (creatinine, glucose, total protein, blood urea nitrogen [BUN], total carbon dioxide [CO₂], albumin, total bilirubin, alkaline phosphatase, and aspartate transaminase [AST] and alanine transaminase [ALT]) and electrolytes (total calcium, chloride, potassium, sodium)
- Calculated creatinine clearance
- Complete blood count (CBC), including platelets, ANC & HGB
- Serum or urine pregnancy test for female patients of childbearing potential
- Documentation of commitment to abstinence for female patients of childbearing potential OR use of appropriate contraception

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- Documentation of commitment to abstinence from heterosexual intercourse for male patients OR commitment to use latex condoms with heterosexual intercourse with females of childbearing potential

7.2 ON TREATMENT

7.2.1 Cycles 1-2

On Day 1 of each treatment cycle, the following assessments/treatment administrations will occur: (For Cycle 1 Day 1 only, required tests do not need to be repeated if done within 7 days prior.)

- Blood pressure
- Weight [kg]
- Physical examination
- Karnofsky Performance Status (KPS)
- Complete metabolic profile (CMP) will include: serum chemistries (creatinine, glucose, total protein, blood urea nitrogen [BUN], total carbon dioxide [CO₂], albumin, total bilirubin, alkaline phosphatase, and aspartate transaminase [AST] and alanine transaminase [ALT]) and electrolytes (total calcium, chloride, potassium, sodium)
- CBC (including platelets, ANC & HGB)
- Blood collection for correlative studies (Cycle 1)
- Concomitant medications
- Collection of AEs
- Gemcitabine administration
- Cisplatin administration following appropriate hydration.
- Correlative studies: Submission of unstained slides from archived tumor sample (Cycle 1 Day 1 only)

On Day 8 of each treatment cycle, the following assessments/treatment administrations will occur:

- Blood pressure
- Weight [Kg]
- Abbreviated physical examination targeted to signs and symptoms
- Karnofsky Performance Status (KPS)
- CBC (including platelets, ANC & HGB)
- Concomitant medications
- Collection of AEs
- Gemcitabine administration

7.2.2 Cycles 3-6

On Day 1 of each treatment cycle, the following assessments/treatment administrations will occur:

- Blood pressure
- Weight [Kg]
- Physical examination
- Karnofsky Performance Status (KPS)
- Complete metabolic profile (CMP) will include: serum chemistries (creatinine, glucose, total protein, blood urea nitrogen [BUN], total carbon dioxide [CO₂], albumin, total bilirubin, alkaline

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phosphatase, and aspartate transaminase [AST] and alanine transaminase [ALT]) and electrolytes (total calcium, chloride, potassium, sodium)

- Liver function tests (AST, ALT, T. bilirubin) will be evaluated for every subject prior to administration of ipilimumab. Blood samples must be collected and analyzed within 3 days prior to dosing.
- TSH
- CBC (including platelets, ANC & HGB)
- Blood collection for correlative studies. (Cycles 3 and 6)
- Concomitant medications
- Collection of AEs
- Serum or urine pregnancy test within 72 hours of first dose of ipilimumab
- Gemcitabine administration
- Cisplatin administration following appropriate hydration
- Ipilimumab administration

On Day 8 of each treatment cycle, the following assessments/treatment administrations will occur:

- Blood pressure
- Weight [Kg]
- Karnofsky Performance Status (KPS)
- Abbreviated physical examination targeted to signs and symptoms
- CBC (including platelets, ANC & HGB)
- Concomitant medications
- Collection of AEs
- Gemcitabine administration for all patients.

7.2.3 Restaging Radiographic Examinations

A CT scan of the chest, abdomen, and pelvis (and bone scan if clinically indicated) will be performed after cycle 2 and after cycle 6. During the maintenance phase with single-agent ipilimumab, patients will undergo restaging CT scans (and bone scans if clinically indicated) every 3 months, until the time of progression.

7.2.4 Maintenance Phase

Day 1 of each cycle

Patients achieving at least stable disease after 6 cycles of “induction therapy” will proceed with single-agent ipilimumab maintenance given once every 3 months. The following assessments will occur on Day 1 of each maintenance cycle:

- Blood pressure
- Weight [Kg]
- Physical examination
- Karnofsky Performance Status (KPS)
- Complete metabolic profile (CMP) will include: serum chemistries (creatinine, glucose, total protein, blood urea nitrogen [BUN], total carbon dioxide [CO₂], albumin, total bilirubin, alkaline phosphatase, and aspartate transaminase [AST] and alanine transaminase [ALT]) and electrolytes (total calcium, chloride, potassium, sodium)

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- Liver function tests (AST, ALT, T. bilirubin) will be evaluated for every subject prior to administration of ipilimumab. Blood samples must be collected and analyzed within 3 days prior to dosing.
- TSH
- CBC (including platelets, ANC & HGB)
- Blood collection for correlative studies (Maintenance Cycle 1 Day 1 Only)
- Concomitant medications
- Collection of AEs
- Review of restaging CT of the chest, abdomen, and pelvis (performed prior to initiation of each subsequent cycle)
- Ipilimumab administration.

Day 30 ± 7 days

- Blood pressure
- Weight [kg]
- Physical examination
- Karnofsky Performance Status (KPS)
- Complete metabolic profile (CMP) will include: serum chemistries (creatinine, glucose, total protein, blood urea nitrogen [BUN], total carbon dioxide [CO₂], albumin, total bilirubin, alkaline phosphatase, and aspartate transaminase [AST] and alanine transaminase [ALT]) and electrolytes (total calcium, chloride, potassium, sodium)
- CBC (including platelets, ANC & HGB)
- Concomitant medications
- Collection of AEs

Day 60 ± 7 days

- Blood pressure
- Weight [kg]
- Physical examination
- Karnofsky Performance Status (KPS)
- Complete metabolic profile (CMP) will include: serum chemistries (creatinine, glucose, total protein, blood urea nitrogen [BUN], total carbon dioxide [CO₂], albumin, total bilirubin, alkaline phosphatase, and aspartate transaminase [AST] and alanine transaminase [ALT]) and electrolytes (total calcium, chloride, potassium, sodium)
- CBC (including platelets, ANC & HGB)
- Concomitant medications
- Collection of AEs

7.3 TREATMENT DISCONTINUATION

A patient will be discontinued from the treatment under the following circumstances:

- If there is evidence of progressive disease (See Section 8.0).
- If the attending physician thinks a change of therapy would be in the best interest of the patient.
- If the drug(s) exhibit(s) unacceptable adverse event.

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- If a patient becomes pregnant.
- Treatment interruption for greater than 21 days due to treatment related adverse event.
- Patients can stop participating at any time. However, if they decide to stop participating in the study, patients will continue to be followed for disease progression and survival.

7.4 END OF TREATMENT EVALUATIONS: ~30 days (± 7 days) post last therapy

At the end of treatment or if the patient withdraws from the study, the following assessments/treatment administrations will occur:

- Blood pressure
- Weight [Kg]
- Physical examination
- Karnofsky Performance Status (KPS)
- Complete metabolic profile (CMP) will include: serum chemistries (creatinine, glucose, total protein, blood urea nitrogen [BUN], total carbon dioxide [CO₂], albumin, total bilirubin, alkaline phosphatase, and aspartate transaminase [AST] and alanine transaminase [ALT]) and electrolytes (total calcium, chloride, potassium, sodium)
- CBC (including platelets, ANC & HGB)
- Blood collection for correlative studies (At the time the patient progresses)
- Concomitant medications
- Collection of AEs
- Radiological assessments if >28 days since last assessment.
- Patients will continue to be followed until resolution or stabilization of any treatment-related toxicities.

7.5 FOLLOW-UP:

Patients proceeding with single-agent maintenance ipilimumab will be followed as described for progression. Patients discontinuing treatment for reasons other than tumor progression will also be followed for progression.

The Investigator or designees will make every possible attempt every 3 months (± 7 days), for 2 years from completion of protocol therapy, every 6 months (± 7 days) for years 3 - 5, and annually thereafter, to contact the patient or family to obtain the survival information of the patient and start date of additional anticancer treatment.

7.6 END OF STUDY:

Patients will be considered off study if any of the following occur:

1. Termination of the study
2. Withdrawal of consent (patient will not be contacted and no further information will be collected). If the patient withdraws consent, then no additional data will be collected without his/her explicit consent; all data collected prior to withdrawal of consent may be used in the data analysis. The collection of date of death and cause of death (if available) will be collected in the study since survival is an endpoint.
3. Lost to follow-up; 3 attempts should be documented in the patient's source document before the site considers the patient as lost to follow-up.
4. Death

8.0 CRITERIA FOR DISEASE EVALUATION

For the current study, response assessments will be made both using the Immune Related Response Criteria, and using RECIST v1.0, allowing additional comparisons among these criteria for disease response assessment. The same measurable and non-measurable lesions will be followed by both RECIST & irRC.

8.1 Immune Related Response Criteria:

This study will utilize the Immune Related Response Criteria (irRC). These response criteria were developed to overcome the variable and unusual patterns of response to immunotherapeutic agents, in particular, ipilimumab²². The development of the guidelines were prompted by observations, mostly in patients with metastatic melanoma, of initial disease progression followed by later response, late responses, and mixed responses with an overall decrease in tumor burden.

8.1.1 Antitumor response based on total measurable tumor burden

For the irRC, only index and measurable new lesions are taken into account (in contrast to conventional WHO criteria, which do not require the measurement of new lesions, nor do they include new lesion measurements in the characterization of evolving tumor burden). At the baseline tumor assessment, the sum of the products of the two largest perpendicular diameters (SPD) of all index lesions (five lesions per organ, up to 10 visceral lesions) is calculated. At each subsequent tumor assessment, the SPD of the index lesions and of new, measurable lesions (up to 5 new lesions per organ; 10 visceral lesions) are added together to provide the total tumor burden: $\text{Tumor Burden} = \text{SPD}_{\text{index lesions}} + \text{SPD}_{\text{new, measurable lesions}}$

Table 5: Comparison of WHO and irRC criteria

	WHO	irRC
New, measurable lesions	Always represent PD	Incorporated into tumor burden
New, nonmeasurable lesions	Always represent PD	Do not define progression (but preclude irCR)
Non-index lesions	Changes contribute to defining BOR of CR, PR, SD, and PD	Contribute to defining irCR (complete disappearance required)
CR	Disappearance of all lesions in two consecutive observations not less than 4 wk apart	Disappearance of all lesions in two consecutive observations not less than 4 wk apart
PR	≥50% decrease in SPD of all index lesions compared with baseline in two observations at least 4 wk apart, in absence of new lesions or unequivocal progression of non-index lesions	≥50% decrease in tumor burden compared with baseline in two observations at least 4 wk apart
SD	50% decrease in SPD compared with baseline cannot be established nor 25% increase compared with nadir, in absence of new lesions or unequivocal progression of non-index lesions	50% decrease in tumor burden compared with baseline cannot be established nor 25% increase compared with nadir
PD	At least 25% increase in SPD compared with nadir and/or unequivocal progression of non-index lesions and/or appearance of new lesions (at any single time point)	At least 25% increase in tumor burden compared with nadir (at any single time point) in two consecutive observations at least 4 wk apart

8.1.2 Time-point response assessment using irRC

Percentage changes in tumor burden per assessment time point describe the size and growth kinetics of both conventional and new, measurable lesions as they appear. At each tumor assessment, the response in index and new, measurable lesions is defined based on the change in tumor burden (after ruling out immune-related progressive disease [irPD]). Decreases in tumor burden must be assessed relative to baseline measurements (i.e., the SPD of all index lesions at screening). The irRC were derived from WHO criteria and, therefore, the thresholds of response remain the same. However, the irRC response categories have been modified from those of WHO criteria as detailed in Section 8, Tables 5 and 6.

8.1.3 Overall response using the irRC

The sum of the products of diameters at tumor assessment using the immune-related response criteria (irRC) for progressive disease incorporates the contribution of new measurable lesions. Each net Percentage Change in Tumor Burden per assessment using irRC criteria accounts for the size and growth kinetics of both old and new lesions as they appear.

Definition of Index Lesions Response Using irRC

- **irComplete Response (irCR):** Complete disappearance of all *index* lesions. This category encompasses exactly the same subjects as “CR” by the mWHO criteria.
- **irPartial Response (irPR):** Decrease, relative to baseline, of 50% or greater in the sum of the products of the two largest perpendicular diameters of all *index* and all new measurable lesions (i.e., Percentage Change in Tumor Burden). Note: the appearance of new measurable lesions is factored into the overall tumor burden, but does not automatically qualify as progressive disease until the SPD increases by $\geq 25\%$ when compared to SPD at nadir.
- **irStable Disease (irSD):** Does not meet criteria for irCR or irPR, in the absence of progressive disease.
- **irProgressive Disease (irPD):** At least 25% increase Percentage Change in Tumor Burden (i.e., taking sum of the products of all *index* lesions and any new lesions) when compared to SPD at nadir.

Definition of Non-Index Lesions Response Using irRC

- **irComplete Response (irCR):** Complete disappearance of all *non-index* lesions. This category encompasses exactly the same subjects as “CR” by the mWHO criteria.
- **irPartial Response (irPR) or irStable Disease (irSD):** *non-index* lesion(s) are not considered in the definition of PR, these terms do not apply.
- **irProgressive Disease (irPD):** Increases in number or size of *non-index* lesion(s) does not constitute progressive disease unless/until the Percentage Change in Tumor Burden increases by 25% (i.e., the SPD at nadir of the index lesions increases by the required amount).

Impact of New Lesions on irRC

New lesions in and by themselves do not qualify as progressive disease. However, their contribution to total tumor burden is included in the SPD, which in turn feeds into the irRC criteria for tumor response. Therefore, new non-measurable lesions will not discontinue any subject from the study.

Definition of Overall Response Using irRC

Overall response using irRC will be based on these criteria (see Section 8, Table 6):

- **Immune-Related Complete Response (irCR):** Complete disappearance of *all* tumor lesions (index and non-index together with no new measurable/unmeasurable lesions) for at least 4 weeks from the date of documentation of complete response.
- **Immune-Related Partial Response (irPR):** The sum of the products of the two largest perpendicular diameters of all index lesions is measured and captured as the SPD baseline. At each subsequent tumor assessment, the sum of the products of the two largest perpendicular diameters of all index lesions and of new measurable lesions are added together to provide the Immune Response Sum of Product Diameters (irSPD). A decrease, relative to baseline of the irSPD compared to the previous SPD baseline, of 50% or greater is considered an immune Partial Response (irPR).
- **Immune-Related Stable Disease (irSD):** irSD is defined as the failure to meet criteria for immune complete response or immune partial response, in the absence of progressive disease.
- **Immune-Related Progressive Disease (irPD):** It is recommended in difficult cases to confirm PD by serial imaging. Any of the following will constitute progressive disease:
 - At least 25% increase in the sum of the products of all index lesions over nadir SPD calculated for the index lesions.
 - At least a 25% increase in the sum of the products of all index lesions and new measurable lesions (irSPD) over the baseline SPD calculated for the index lesions.

Immune-Related Best Overall Response Using irRC (irBOR)

irBOR is the best confirmed irRC overall response over the study as a whole, recorded between the date of first dose until the last tumor assessment before subsequent therapy (except for local palliative radiotherapy for painful bone lesions) for the individual subject in the study. For the assessment of irBOR, all available assessments per subject are considered.

irCR or irPR determinations included in the irBOR assessment must be confirmed by a second (confirmatory) evaluation meeting the criteria for response and performed no less than 4 weeks after the criteria for response are first met.

Table 6: Derivation of irRC overall responses

Measurable response	Nonmeasurable response		Overall response
Index and new, measurable lesions (tumor burden), *%	Non-index lesions	New, nonmeasurable lesions	Using irRC
↓100	Absent	Absent	irCR [†]
↓100	Stable	Any	irPR [†]
↓100	Unequivocal progression	Any	irPR [†]
↓≥50	Absent/Stable	Any	irPR [†]
↓≥50	Unequivocal progression	Any	irPR [†]
↓<50 to <25↑	Absent/Stable	Any	irSD
↓<50 to <25↑	Unequivocal progression	Any	irSD
≥25	Any	Any	irPD [†]

*Decreases assessed relative to baseline (scan prior to start of any protocol therapy), including measurable lesions only

[†]Assuming response (irCR) and progression (irPD) are confirmed by a second, consecutive assessment at least 4 wk apart.

8.1.4 Progression criteria for the current study

Ipilimumab is expected to trigger immune-mediated responses, which require activation of the immune system prior to the observation of clinical responses. Such immune activation may take weeks to months to be evident. Some patients may have objective volume increase of tumor lesions or other disease parameters (based on study indication, i.e., hematologic malignancies) within 12 weeks following start of ipilimumab dosing. Such patients may not have had sufficient time to develop the required immune activation or, in some patients, tumor volume or other disease parameter increases may represent infiltration of lymphocytes into the original tumor or blood. In conventional studies, such tumor volume or relevant laboratory parameter increases during the first 12 weeks of the study would constitute progressive disease (PD) and lead to discontinuation of imaging to detect response, thus disregarding the potential for subsequent immune-mediated clinical response.

Therefore, patients with tumor volume increase detected or lack of laboratory parameter response documentation prior to week 12 but without rapid clinical deterioration should continue to be treated with ipilimumab and clinically observed with a stringent imaging schedule to allow detection of a subsequent tumor response. This will improve the overall assessment of the clinical activity of ipilimumab and more likely capture its true potential to induce clinical responses.

On the current study, patients will undergo a restaging CT scan after cycle 2 and after cycle 6. However, patients with evidence of disease progression (in the absence of rapid clinical deterioration) on the post-cycle 2 CT scan will not be taken off study, as they will have not yet started ipilimumab.

Furthermore, as durable disease stabilization and/or objective tumor response can be seen in other advanced solid tumors after early progression before 12 weeks of ipilimumab treatment, it is recommended that, in the absence of treatment-limiting toxicities (e.g., serious irAEs), symptomatic progression, or deterioration in functional status, all four doses of ipilimumab be administered (cycles 3-6).

Based on clinical experience in ongoing and completed ipilimumab studies, the following recommendations apply for subject management in light of the post-cycle 6 or later tumor assessments:

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- The appearance of new lesions in subjects with other stable or shrinking baseline tumor burden may be experiencing clinical benefit and should continue in follow-up and/or maintenance therapy before alternative anti-cancer agents are considered. These subjects can be seen to have continued tumor shrinkage in follow-up scans.
- As long as overall tumor burden is stable or decreasing, subjects should remain in follow-up and/or maintenance, even in the presence of new lesions.
- Clinical progression warranting alternative anti-cancer treatment should be considered only in subjects whose overall tumor burden appears to be substantially increased (e.g., meets criteria for irPD) and/or in subjects whose performance status is decreased.

Patients with disease progression on the post-cycle 6 scan (in the absence of symptomatic/functional deterioration) should have a confirmatory CT scan at least 4 weeks later as per the irRC.

8.1.5 Definition of Measurable and Non-Measurable Lesions

Measurable Lesions are lesions that can be accurately measured in two perpendicular diameters, with at least one diameter ≥ 20 mm and the other dimension ≥ 10 mm (10 mm x 10 mm for spiral CT). The area will be defined as the product of the largest diameter with its perpendicular. Skin lesions can be considered measurable.

Non-Measurable (evaluable) Lesions are all other lesions, including unidimensionally measurable disease and small lesions (lesions without at least one diameter ≥ 20 mm), and any of the following:

- Lesions occurring in a previously irradiated area (unless they are documented as new lesions since the completion of radiation therapy), bone lesions, leptomeningeal disease, ascites, pleural or pericardial effusion, lymphangitis cutis/pulmonis, abdominal masses that are not pathologically/cytologically confirmed and followed by imaging techniques and cystic lesions.
- All measurable and non-measurable lesions should be measured at screening and at the defined tumor assessment time points (see Section 7, Study Calendar & Evaluations). Extra assessments may be performed, as clinically indicated, if there is a suspicion of progression.

8.2 Definitions Associated with Response Evaluation Criteria in Solid Tumors (RECIST v1.0):

- 8.2.1** 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.
- 8.2.2** Measurable lesions - lesions that can be accurately measured in at least one dimension with longest diameter (LD) >20 mm using conventional techniques or >10 mm with spiral CT scan.
- 8.2.3** 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.

8.2.4 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 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.

8.2.5 Response Criteria

Table 7: Response Criteria for Target Lesions

Response	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
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
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

Table 8: Response Criteria for Non-Target Lesions

Response	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) and/or maintenance of tumor marker level above the normal limits
Progressive Disease (PD)	Appearance of one or more new lesions and/or unequivocal progression of existing non-target lesions ⁽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 the Sponsor Investigator).

8.2.6 Evaluation of best overall response

The objective response rate is the proportion of all patients with confirmed PR or CR according to RECIST v1.0, from the start of treatment until disease progression/recurrence (taking as reference for progressive disease the smallest measurements recorded since the start of treatment).

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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.

Table 9: Evaluation of best overall response

Target Lesions	Non-Target lesion	New Lesion	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 Definitions Associated with Response Evaluation Criteria in Solid Tumors (RECIST v1.0)

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.

9.0 BIOLOGICAL CORRELATIVES

See Correlative Science Plan (Attachment)

10.0 CLINICAL TRIAL MATERIALS (CTM) INFORMATION & ADVERSE EVENTS MANAGEMENT

10.1 Ipilimumab:

The investigational product is defined as a pharmaceutical form of an active ingredient being tested as a reference in the study, whether blinded or unblinded. In this study, the investigational product is ipilimumab.

Other medications used in the study as support or escape medication for preventative, diagnostic, or therapeutic reasons, as components of the standard of care for a given diagnosis, are considered noninvestigational products. In this protocol, noninvestigational product(s) is/are: gemcitabine, cisplatin.

Identification

Ipilimumab is available in concentrations of 5 mg/mL (50 mg/10 mL and 200 mg/40 mL). The sterile solution in the vial is clear and colorless. Ipilimumab is administered via intravenous infusion only.

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Packaging and Labeling

BMS will provide ipilimumab at no cost for this study. Ipilimumab will be provided in open-label containers. The labels will contain the protocol prefix, batch number, content, storage conditions, and dispensing instructions along with the Investigational New Drug (IND) caution statement.

Storage, Handling, and Dispensing**Storage**

Ipilimumab must be stored in a secure area according to local regulations. The investigator must ensure that it is stored at a temperature $\pm 2^{\circ}\text{C}$ and $\pm 8^{\circ}\text{C}$.

Handling and Disposal

As with all injectable drugs, care should be taken when handling and preparing ipilimumab. Whenever possible, ipilimumab should be prepared in a laminar flow hood or safety cabinet using standard precautions for the safe handling of intravenous agents applying aseptic technique. Latex gloves are required. If ipilimumab concentrate or solution comes in contact with skin or mucosa, immediately and thoroughly wash with soap and water. After final drug reconciliation, unused ipilimumab solution should be disposed at the site following procedures for the disposal of anticancer drugs.

Dispensing

It is the responsibility of the investigator to ensure that ipilimumab is only dispensed to study subjects. The ipilimumab must be dispensed only from official study sites by authorized personnel according to local regulations.

Drug Ordering and Accountability

Orders, See SPM for instruction on drug ordering.

Ipilimumab Accountability

It is the responsibility of the investigator to ensure that a current record of ipilimumab disposition is maintained at each study site where ipilimumab is inventoried and disposed. Records or logs must comply with applicable regulations and guidelines, and should include:

- Amount received and placed in storage area.
- Amount currently in storage area.
- Label ID number or batch number and use date or expiry date.
- Dates and initials of person responsible for each ipilimumab inventory entry/movement.
- Amount dispensed to and returned by each subject, including unique subject identifiers.
- Amount transferred to another area/site for dispensing or storage.
- Non-study disposition (e.g., lost, wasted, broken).
- Amount destroyed at study site.

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Ipilimumab Destruction

If ipilimumab is to be destroyed on site, it is the investigator's responsibility to ensure that arrangements have been made for disposal and that procedures for proper disposal have been established according to applicable regulations, guidelines, and institutional procedures. Appropriate records of the disposal must be maintained.

Preparation and Administration

Refer to the package insert for YERVOY® (ipilimumab) for detailed preparation and administration guidelines.

The supplies needed for ipilimumab preparation and administration include calibrated syringes and infusion containers. Ipilimumab is to be administered as an IV infusion using a volumetric pump through a 0.2 or 1.2 micrometer in-line filter (supplied by site) at the 10 mg/kg dose. See the current Investigator Brochure for additional information on allowable filter types.

Ensure that the ipilimumab solution is clear colorless, essentially free from particulate matter on visual inspection. If multiple vials are needed for a subject, it is important to use a separate sterile syringe and needle for each vial to prevent problems such as dulling of needle tip, stopper coring, repeated friction of plunger against syringe barrel wall, etc.

Preparation of Solution

As ipilimumab is stored at refrigerated temperatures (2-8°C), allow the appropriate number of vials of ipilimumab to stand at room temperature for approximately five minutes.

Aseptically withdraw the required volume of ipilimumab solution and transfer to an intravenous bag. Do not draw into each vial more than once.

Dilute with 0.9% Sodium Chloride Injection, USP or 5% Dextrose Injection, USP to prepare a diluted solution with a final concentration ranging from 1 mg/mL to 2 mg/ML.

Mix by GENTLY inverting several times. DO NOT shake.

Visually inspect the final solution. If the initial diluted solution or final dilution for infusion is not clear or contents appear to contain precipitate, the solution should be discarded.

Store diluted solution for no more than 24 hours under refrigeration (2-8°C) or at room temperature (20-25 °C). Any partial vials should be safely discarded and should not be stored for reuse.

Administration Instructions

Ipilimumab should be administered under the supervision of a physician experienced in the use of intravenous (IV) agents. Ipilimumab is administered as an IV infusion only.

The infusion must be completed in 90 minutes with a 10 ml normal saline flush at the end. The ratio and rate will be specified in the pharmacy manual. The total dose must be calculated using the most recent subject weight (obtained within 3 days of the dosing visit, and prior to the infusion).

Side Effects:

Among all treated subjects, the most frequently reported treatment-related AEs of any grade included fatigue (27.8%), diarrhea (27.5%), nausea (23.4%), rash (21.8%), pruritus (19.9%), pyrexia (11.9%), and vomiting (11.7%).

Similarly, among subjects treated with ipilimumab at 10 mg/kg, the most frequently reported treatment-related AEs of any grade included diarrhea (38.1%), fatigue (30.5%), rash (34.5%), pruritus (29.8%), nausea (17.6%), pyrexia (12.3%), vomiting (10.9%), and colitis (10.2%).

Among all 2901 treated subjects, SAEs considered possibly, probably, or definitely related to study drug were reported for 20.5% of subjects. Drug-related SAEs reported in at least 1% of the 2901 subjects included diarrhea (5.8%), colitis (4.7%), ALT increased (2.3%), AST increased (2.2%), pyrexia (1.6%), and vomiting (1.3%). Among the 658 subjects who received ipilimumab at 10 mg/kg, SAEs considered possibly, probably, or definitely related to study drug were reported for 27.2% of subjects. Drug-related SAEs reported in at least 1% of the 658 subjects treated at 10 mg/kg included diarrhea (8.5%), colitis (7.0%), vomiting (2.1%), AST increased (2.1%), ALT increased (2.0%), autoimmune hepatitis (2.0%), pyrexia (1.8%), hypopituitarism (1.7%), dehydration (1.7%), nausea (1.2%), abdominal pain (1.1%), and GI perforation (1.7%).

10.2 Cisplatin:

<u>Drug Name:</u>	Cisplatin Other: Platinol; Cis-diamminedichloroplatinum
<u>Classification:</u>	Alkylating agent
<u>Action:</u>	Cisplatin forms covalent bonds with nucleophilic sites on guanine present in all DNA. As cisplatin is a bifunctional agent, it is able to bind to 2 sites in a DNA strand. This results in the formation of inter- and intra-chain cross-linkings, which interferes with cellular transcription and replication. Regulatory mechanisms detect the abnormal DNA and so activate a chain of responses to try and correct it. This, ultimately, causes cell death (apoptosis).
<u>Availability:</u>	Cisplatin is commercially available.
<u>Storage:</u>	Cisplatin Injection is a sterile, multi-dose vial without preservatives. Store at 15° to 25°C (59° to 77°F). Note: Do not refrigerate. Protect unopened container from light. The cisplatin remaining in the amber vial following initial entry is stable for 28 days protected from light or for 7 days under fluorescent room light.
<u>Reconstitution:</u>	The aqueous solution should be used intravenously only and should be administered by IV. Cisplatin is a cytotoxic chemotherapeutic agent.

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Appropriate precautions for hazardous drug handling should be taken during handling, preparation, administration and disposal of this agent. As with other potentially toxic compounds, caution should be exercised in handling the aqueous solution. Skin reactions associated with accidental exposure to cisplatin may occur. The use of gloves is recommended. If cisplatin contacts the skin or mucosa, immediately and thoroughly wash the skin with soap and water and flush the mucosa with water.

Administration: Cisplatin will be administered IV according to institutional guidelines.

Hydration

Hydration for cisplatin can be administered at the discretion of the treating physician and according to institutional standards.

Side Effects:

Nephrotoxicity: Dose related and cumulative renal insufficiency is the major dose-limiting toxicity. Renal toxicity has been noted in 28-36% of patients treated with a single dose of 50 mg/m². It is first noted during the second week after a dose and is manifested by elevations in BUN and creatinine, serum uric acid, and/or a decrease in creatinine clearance.

Note: Renal toxicity becomes more prolonged and severe with repeated courses of the drug. Renal function must return to normal before another dose of cisplatin can be given.

Ototoxicity: Ototoxicity has been observed in up to 31% of patients treated with a single dose of cisplatin 50 mg/m², and is manifested by tinnitus and/or hearing loss in the high frequency range (4,000 to 8,000 Hz). Decreased ability to hear normal conversational tones may occur occasionally. Deafness after the initial dose of cisplatin has been reported rarely. Ototoxic effects may be more severe in children receiving cisplatin. Hearing loss can be unilateral or bilateral and tends to become more frequent and severe with repeated doses. Ototoxicity may be enhanced with prior or simultaneous cranial irradiation. It is unclear whether cisplatin-induced ototoxicity is reversible. Ototoxic effects may be related to the peak plasma concentration of cisplatin. Vestibular toxicity has also been reported. Ototoxicity may become more severe in patients being treated with other drugs with nephrotoxic potential. Patients should be questioned regarding any history of hearing deficit.

Hematologic: Myelosuppression occurs in 25% to 30% of patients treated with cisplatin. The nadirs in circulating platelets and leukocytes occur between days 18 to 23 (range 7.5 to 45) with most patients recovering by day 39 (range 13 to 62). Leukopenia and thrombocytopenia are more pronounced at higher doses (>50 mg/m²). Anemia (decrease of 2 g hemoglobin/100 mL) occurs at approximately the same frequency and with the same timing as leukopenia and thrombocytopenia. Fever and infections have also been reported in patients with neutropenia.

In addition to anemia secondary to myelosuppression, a Coombs' positive hemolytic anemia has been reported. In the presence of cisplatin hemolytic anemia,

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a further course of treatment may be accompanied by increased hemolysis, and this risk should be weighed by the Treating Physician.

The development of acute leukemia coincident with the use of cisplatin has rarely been reported in humans. In these reports, cisplatin was generally given in combination with other leukemogenic agents.

Gastrointestinal: Marked nausea and vomiting occur in almost all patients treated with cisplatin, and are occasionally so severe that the drug must be discontinued. Nausea and vomiting usually begin within 1 to 4 hours after treatment and last for 24 hours. Various degrees of vomiting, nausea and/or anorexia may persist for up to 1 week after treatment. Delayed nausea and vomiting (begins or persists 24 hours or more after chemotherapy) has occurred in patients attaining complete emetic control on the day of cisplatin therapy. Diarrhea has also been reported.

Other Toxicities: Vascular toxicities coincident with the use of cisplatin in combination with other antineoplastic agents have been reported rarely. The events are clinically heterogeneous and may include myocardial infarction, cerebrovascular accident, thrombotic microangiopathy (HUS), or cerebral arteritis. Various mechanisms have been proposed for these vascular complications. There are also reports of Raynaud's phenomenon occurring in patients treated with the combination of bleomycin, vinblastine with or without cisplatin. It has been suggested that hypomagnesemia developing coincident with the use of cisplatin may be an added, although not essential, factor associated with this event. However, it is currently unknown if the cause of Raynaud's phenomenon in these cases is the disease, underlying vascular compromise, bleomycin, vinblastine, hypomagnesemia, or a combination of any of these factors.

Serum Electrolyte Disturbances: Hypomagnesemia, hypocalcemia, hyponatremia, hypokalemia, and hypophosphatemia have been reported to occur in patients treated with cisplatin and are probably related to renal tubular damage. Tetany has occasionally been reported in those patients with hypocalcemia and hypomagnesemia. Generally, administering supplemental electrolytes and discontinuing cisplatin restore normal serum electrolyte levels. Inappropriate antidiuretic hormone syndrome has also been reported.

Hyperuricemia: Hyperuricemia has been reported to occur at approximately the same frequency as the increases in BUN and serum creatinine. It is more pronounced after doses greater than 50 mg/m², and peak levels of uric acid generally occur between 3 to 5 days after the dose. Allopurinol therapy for hyperuricemia effectively reduces uric acid levels.

Neurotoxicity: Neurotoxicity, usually characterized by peripheral neuropathies, has been reported. The neuropathies usually occur after prolonged therapy (4 to 7 months); however, neurologic symptoms have been reported to occur after a single dose. Although symptoms and signs of cisplatin neuropathy usually develop during treatment, symptoms of neuropathy may begin 3 to 8 weeks after the last dose of cisplatin, although this is rare. Cisplatin therapy should be discontinued when the

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symptoms are first observed. The neuropathy, however, may progress further even after stopping treatment. Preliminary evidence suggests peripheral neuropathy may be irreversible in some patients. Lhermitte's sign, dorsal column myelopathy, and autonomic neuropathy have also been reported. Loss of taste and seizures have also been reported.

Muscle cramps, defined as localized, painful, involuntary skeletal muscle contractions of sudden onset and short duration, have been reported, and were usually associated in patients receiving a relatively high cumulative dose of cisplatin and with a relatively advanced symptomatic stage of peripheral neuropathy.

Ocular Toxicity: Optic neuritis, papilledema, and cerebral blindness have been reported infrequently in patients receiving standard recommended doses of cisplatin. Improvement and/or total recovery usually occurs after discontinuing cisplatin. Steroids with or without mannitol have been used; however, efficacy has not been established.

Blurred vision and altered color perception have been reported after the use of regimens with higher doses of cisplatin or greater dose frequencies than those recommended in the package insert. The altered color perception manifests as a loss of color discrimination, particularly in the blue-yellow axis. The only finding on funduscopy exam is irregular retinal pigmentation of the macular area.

Anaphylactic-like Reactions: Anaphylactic-like reactions have been occasionally reported in patients previously exposed to cisplatin. The reactions consist of facial edema, wheezing, tachycardia, and hypotension within a few minutes of drug administration. Reactions may be controlled by IV epinephrine with corticosteroids and/or antihistamines as indicated. Patients receiving cisplatin should be observed carefully for possible anaphylactic-like reactions and supportive equipment and medication should be available to treat such a complication.

Hepatotoxicity: Transient elevations of liver enzymes, especially SGOT, as well as bilirubin, have been reported to be associated with cisplatin administration at the recommended doses.

Other Events: Other toxicities reported to occur infrequently are cardiac abnormalities, hiccups, elevated serum amylase, and rash. Alopecia, malaise, and asthenia have been reported as part of post-marketing surveillance.

Local soft tissue toxicity has rarely been reported following extravasation of cisplatin. Severity of the local tissue toxicity appears to be related to the concentration of the cisplatin solution. Infusion of solutions with a cisplatin concentration greater than 0.5 mg/mL may result in tissue cellulitis, fibrosis, and necrosis.

Pregnancy. Cisplatin can cause fetal harm when administered to a pregnant woman. Cisplatin is mutagenic in bacteria and produces chromosome aberrations in animal

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cells in tissue culture. In mice, cisplatin is teratogenic and embryotoxic. If this drug is used during pregnancy or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to the fetus. Patients should be advised to avoid becoming pregnant.

Nursing mothers. Cisplatin has been reported to be found in human milk, patients receiving cisplatin should not breastfeed.

10.3 Gemcitabine:

Drug Name:

Gemcitabine

Other: 2'-deoxy-2',2'-difluorocytidine monohydrochloride, Gemzar

Classification:

Nucleoside analogue

Action:

Gemcitabine is metabolized intracellularly by nucleoside kinases to the active diphosphate (dFdCDP) and triphosphate (dFdCTP) nucleosides. The cytotoxic effect of gemcitabine is attributed to a combination of 2 actions of the diphosphate and the triphosphate nucleosides, which leads to inhibition of DNA synthesis. First, gemcitabine diphosphate inhibits ribonucleotide reductase, which is responsible for catalyzing the reactions that generate the deoxynucleoside triphosphates for DNA synthesis. Inhibition of this enzyme by the diphosphate nucleoside causes a reduction in the concentrations of deoxynucleotides, including dCTP. Second, gemcitabine triphosphate competes with dCTP for incorporation into DNA. The reduction in the intracellular concentration of dCTP (by the action of the diphosphate) enhances the incorporation of gemcitabine triphosphate into DNA (self-potential). After the gemcitabine nucleotide is incorporated into DNA, only 1 additional nucleotide is added to the growing DNA strands. After this addition, there is inhibition of further DNA synthesis. DNA polymerase epsilon is unable to remove the gemcitabine nucleotide and repair the growing DNA strands (masked chain termination).

Availability:

Commercially available and FDA approved for pancreatic cancer. Also, recently approved for locally unresectable or metastatic non-small cell lung cancer in combination with cisplatin.

Storage:

Unopened vials of Gemzar are stable until the expiration date indicated on the package when stored at controlled room temperature 20° to 25°C (68° to 77°F). When prepared as directed, Gemzar solutions are stable for 24 hours at controlled room temperature 20° to 25°C (68° to 77°F). Discard unused portion. Solutions of reconstituted Gemzar should not be refrigerated, as crystallization may occur.

Reconstitution:

The recommended diluent for reconstitution of Gemzar is 0.9% Sodium Chloride Injection without preservatives. Due to solubility considerations, the maximum concentration for Gemzar upon reconstitution is 40 mg/mL.

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Reconstitution at concentrations greater than 40 mg/mL may result in incomplete dissolution, and should be avoided.

To reconstitute, add 5 mL of 0.9% Sodium Chloride Injection to the 200-mg vial or 25 mL of 0.9% Sodium Chloride Injection to the 1-g vial. Shake to dissolve. These dilutions each yield a gemcitabine concentration of 38 mg/mL, which includes accounting for the displacement volume of the lyophilized powder (0.26 mL for the 200-mg vial or 1.3 mL for the 1-g vial). The total volume upon reconstitution will be 5.26 mL or 26.3 mL, respectively. Complete withdrawal of the vial contents will provide 200 mg or 1 g of gemcitabine, respectively. The appropriate amount of drug may be administered as prepared or further diluted with 0.9% Sodium Chloride Injection to concentrations as low as 0.1 mg/mL.

Reconstituted Gemzar is a clear, colorless to light straw-colored solution. After reconstitution with 0.9% Sodium Chloride Injection, the pH of the resulting solution lies in the range of 2.7 to 3.3. The solution should be inspected visually for particulate matter and discoloration, prior to administration, whenever solution or container permit. If particulate matter or discoloration is found, do not administer. Gemzar should be administered by intravenous infusion at a dose of 1000 mg/m² over 30 minutes.

Administration: Gemzar should be administered by intravenous infusion over 30 minutes.

Side Effects: Hematologic: In studies in pancreatic cancer, myelosuppression is the dose-limiting toxicity with Gemzar, but <1% of patients discontinued therapy for either anemia, leukopenia, or thrombocytopenia. Red blood cell transfusions were required by 19% of patients. The incidence of sepsis was less than 1%. Petechiae or mild blood loss (hemorrhage), from any cause, was reported in 16% of patients; less than 1% of patients required platelet transfusions. Patients should be monitored for myelosuppression during Gemzar therapy and dosage modified or suspended according to the degree of hematologic toxicity.

Gastrointestinal: Nausea and vomiting were commonly reported (69%) but were usually of mild to moderate severity. Severe nausea and vomiting (WHO Grade 3-4) occurred in <15% of patients. Diarrhea was reported by 19% of patients, and stomatitis by 11% of patients.

Hepatic: In clinical trials, Gemzar was associated with transient elevations of 1 or both serum transaminases in approximately 70% of patients, but there was no evidence of increasing hepatic toxicity with either longer duration of exposure to Gemzar or with greater total cumulative dose. Serious hepatotoxicity, including liver failure and death, has been reported very rarely in patients receiving Gemzar alone or in combination with other potentially hepatotoxic drugs (see Hepatic under Post-marketing experience, below).

Renal: In clinical trials, mild proteinuria and hematuria were commonly reported. Clinical findings consistent with the Hemolytic Uremic Syndrome

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(HUS) were reported in 6 of 2429 patients (0.25%) receiving Gemzar in clinical trials. Four patients developed HUS on Gemzar therapy, 2 immediately post-therapy. The diagnosis of HUS should be considered if the patient develops anemia with evidence of microangiopathic hemolysis, elevation of bilirubin or lactate dehydrogenase (LDH), reticulocytosis, severe thrombocytopenia, and/or evidence of renal failure (elevation of serum creatinine or BUN). Gemzar therapy should be discontinued immediately. Renal failure may not be reversible even with discontinuation of therapy and dialysis may be required (see Renal under Post-marketing experience, below).

Fever: The overall incidence of fever was 41%. This is in contrast to the incidence of infection (16%) and indicates that Gemzar may cause fever in the absence of clinical infection. Fever was frequently associated with other flu-like symptoms and was usually mild and clinically manageable.

Rash: Rash was reported in 30% of patients. The rash was typically a macular or finely granular maculopapular pruritic eruption of mild to moderate severity involving the trunk and extremities. Pruritus was reported for 13% of patients.

Pulmonary: In clinical trials, dyspnea, unrelated to underlying disease, has been reported in association with Gemzar therapy. Dyspnea was occasionally accompanied by bronchospasm. Pulmonary toxicity has been reported with the use of Gemzar (see Pulmonary under Post-marketing experience, below). The etiology of these effects is unknown. If such effects develop, Gemzar should be discontinued. Early use of supportive care measures may help ameliorate these conditions.

Edema: Edema (13%), peripheral edema (20%), and generalized edema (<1%) were reported. Less than 1% of patients discontinued due to edema.

Flu-like Symptoms: “Flu syndrome” was reported for 19% of patients. Individual symptoms of fever, asthenia, anorexia, headache, cough, chills, and myalgia were commonly reported. Fever and asthenia were also reported frequently as isolated symptoms. Insomnia, rhinitis, sweating, and malaise were reported infrequently. Less than 1% of patients discontinued due to flu-like symptoms.

Infection: Infections were reported for 16% of patients. Sepsis was rarely reported (<1%).

Alopecia: Hair loss, usually minimal, was reported by 15% of patients.

Neurotoxicity: There was a 10% incidence of mild paresthesias and a <1% rate of severe paresthesias.

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Extravasation: Injection-site related events were reported for 4% of patients. There were no reports of injection site necrosis. Gemzar is not a vesicant.

Allergic: Bronchospasm was reported for less than 2% of patients. Anaphylactoid reaction has been reported rarely. Gemzar should not be administered to patients with a known hypersensitivity to this drug (see CONTRAINDICATION in the package insert).

Cardiovascular: During clinical trials, 2% of patients discontinued therapy with Gemzar due to cardiovascular events such as myocardial infarction, cerebrovascular accident, arrhythmia, and hypertension. Many of these patients had a prior history of cardiovascular disease (see Cardiovascular under Post-marketing experience, below).

Post-marketing experience: The following adverse events have been identified during post-approval use of Gemzar. These events have occurred after Gemzar single-agent use and Gemzar in combination with other cytotoxic agents. Decisions to include these events are based on the seriousness of the event, frequency of reporting, or potential causal connection to Gemzar.

Cardiovascular – Congestive heart failure and myocardial infarction have been reported very rarely with the use of Gemzar. Arrhythmias, predominantly supraventricular in nature, have been reported very rarely.

Vascular Disorders – Clinical signs of peripheral vasculitis and gangrene have been reported very rarely.

Skin – Cellulitis and non-serious injection site reactions in the absence of extravasation have been rarely reported. Severe skin reactions, including desquamation and bullous skin eruptions, have been reported very rarely.

Hepatic – Increased liver function tests including elevations in aspartate aminotransferase (AST), alanine aminotransferase (ALT), gamma-glutamyl transferase (GGT), alkaline phosphatase, and bilirubin levels have been reported rarely. Serious hepatotoxicity including liver failure and death has been reported very rarely in patients receiving Gemzar alone or in combination with other potentially hepatotoxic drugs.

Pulmonary – Parenchymal toxicity, including interstitial pneumonitis, pulmonary fibrosis, pulmonary edema, and adult respiratory distress syndrome (ARDS), has been reported rarely following 1 or more doses of Gemzar administered to patients with various malignancies. Some patients experienced the onset of pulmonary symptoms up to 2 weeks after the last Gemzar dose. Respiratory failure and death occurred very rarely in some patients despite discontinuation of therapy.

Renal – Hemolytic-Uremic Syndrome (HUS) and/or renal failure have been reported following 1 or more doses of Gemzar. Renal failure leading to death

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or requiring dialysis, despite discontinuation of therapy, has been rarely reported. The majority of the cases of renal failure leading to death were due to HUS.

Injury, Poisoning, and Procedural Complications – Radiation recall reactions have been reported

Pregnancy

Pregnancy Category D. Gemzar can cause fetal harm when administered to a pregnant woman. Gemcitabine is embryotoxic causing fetal malformations (cleft palate, incomplete ossification) at doses of 1.5 mg/kg/day in mice (about 1/200 the recommended human dose on a mg/m² basis). Gemcitabine is fetotoxic causing fetal malformations (fused pulmonary artery, absence of gall bladder) at doses of 0.1 mg/kg/day in rabbits (about 1/600 the recommended human dose on a mg/m² basis). Embryotoxicity was characterized by decreased fetal viability, reduced live litter sizes, and developmental delays. There are no studies of Gemzar in pregnant women. If Gemzar is used during pregnancy, or if the patient becomes pregnant while taking Gemzar, the patient should be apprised of the potential hazard to the fetus.

Nursing mothers. It is not known whether Gemzar or its metabolites are excreted in human milk. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions from Gemzar in nursing infants, the mother should be warned and a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother and the potential risk to the infant.

11.0 REPORTING ADVERSE EVENTS & SERIOUS ADVERSE EVENTS

11.1 Definitions of Adverse Events:

11.1.1 Adverse Event (AE)

Any untoward medical occurrence in a patient or clinical trial subject administered an investigational product and which does not necessarily have a causal relationship with the treatment. An adverse event (AE) can, therefore, be any unfavorable and unintended sign (including an abnormal finding), symptom, or disease temporally associated with the use of an investigational product, whether or not related to the investigational product.

11.1.2 Serious Adverse Event (SAE)

A serious adverse event is any untoward medical occurrence resulting in one or more of the following:

- Results in death

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- Is life-threatening (defined as an event in which the patient was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe)
- Requires inpatient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity
- Is a congenital anomaly or birth defect
- Is an important medical event (defined as a medical event(s) that may not be immediately life-threatening or result in death or hospitalization but, based upon appropriate medical and scientific judgment, may jeopardize the patient or may require intervention (e.g., medical, surgical) to prevent one of the other serious outcomes listed in the definition above). Examples of such events include, but are not limited to, intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions not resulting in hospitalization; or the development of drug dependency or drug abuse.

11.1.3 Unexpected Adverse Event

An adverse event not mentioned in the Investigator's Brochure or package insert or the specificity or severity of which is not consistent with the Investigator's Brochure or package insert.

11.2 Adverse Event (AE) Reporting:

Adverse events (AEs) will be recorded from the time of consent and for at least 30 days after treatment discontinuation, regardless of whether or not the event(s) are considered related to trial medications. All AEs considered related to trial medication will be followed until resolution, return to baseline, or deemed clinically insignificant, even if this occurs post-trial.

11.3 Serious Adverse Event (SAE) Reporting:

11.3.1 Study Center (Site) Requirements for Reporting SAEs

Investigators and other site personnel must report any SAEs occurring during the course of the study within one business day of discovery of the event. This includes events both related and unrelated to the investigational product.

The definition of "related" being that there is a reasonable possibility the drug caused the adverse experience.

Unrelated	The Adverse Event is <i>clearly not related</i> to the investigational agent(s)
Unlikely	The Adverse Event is <i>doubtfully related</i> to the investigational agent(s)
Possible	The Adverse Event <i>may be related</i> to the investigational agent(s)
Probable	The Adverse Event is <i>likely related</i> to the investigational agent(s)
Definite	The Adverse Event is <i>clearly related</i> to the investigational agent(s)

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The completed SAE Report Form (see Study Procedure Manual) must be faxed to Hoosier Cancer Research Network within 1 working day of discovery of the event. The investigator is responsible for informing the IRB and/or the Regulatory Authority of the SAE as per local requirements.

The original copy of the SAE Report and the fax confirmation sheet must be kept within the Trial Master File at the study site.

Follow-up information will be faxed to the Hoosier Cancer Research Network, using a new SAE Report Form stating that this is a follow-up to the previously reported SAE and giving the date of the original report. Each re-occurrence, complication, or progression of the original event should be reported as a follow-up to that event regardless of when it occurs. The follow-up information should describe whether the event has resolved or continues, if and how it was treated, whether the blind was broken or not (if applicable), and whether the patient continued or withdrew from study participation.

11.3.2 Death and Immediately Life-Threatening Events

Any death and immediately life-threatening event from any cause while a patient is receiving trial treatment on this protocol or up to 30 days after the last dose of trial treatment, or any death and immediately life-threatening event occurring more than 30 days after trial treatment has ended but which is felt to be treatment related must be reported **within one working day of discovery of the event**. All deaths must be reported primarily for the purposes of SAE reporting; however, deaths due unequivocally to progression are not SAEs.

Your local IRB should be notified and their reporting procedure followed. The completed SAE Reporting Form should be faxed to Hoosier Cancer Research Network **within one working day of discovery of the event**.

11.3.3 HCRN Requirements for Reporting SAEs

The Hoosier Cancer Research Network will report any possibly related SAE to BMS **within one working day** of receipt of the SAE Reporting Form and to regulatory authorities (FDA) per federal guidelines.

The Hoosier Cancer Research Network will fax a MedWatch to BMS and will provide follow-up information as reasonably requested.

11.4 IND Safety Reports Unrelated to This Trial

IND safety reports not occurring on this trial but involving the study intervention (outside SAEs) received from outside sources will be reviewed by the Sponsor Investigator and will be forwarded to participating sites for submission to their Institutional Review Boards per their guidelines.

11.5 Pregnancy

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Sexually active WOCBP must use an effective method of birth control during the course of the study, in a manner such that risk of failure is minimized.

Before study enrollment, WOCBP must be advised of the importance of avoiding pregnancy during study participation and the potential risk factors for an unintentional pregnancy. The subject must sign an informed consent form documenting this discussion.

All WOCBP MUST have a negative pregnancy test within 72 hours before receiving ipilimumab. The minimum sensitivity of the pregnancy test must be 25 IU/L or equivalent units of HCG. If the pregnancy test is positive, the subject must not receive ipilimumab and must not be enrolled in the study.

In addition, all WOCBP should be instructed to contact the investigator immediately if they suspect they might be pregnant (e.g., missed or late menstrual period) at any time during study participation.

If, following initiation of the investigational product, it is subsequently discovered that a study subject is pregnant or may have been pregnant at the time of investigational product exposure, including during at least 6 half-lives after product administration, the investigational product will be permanently discontinued in an appropriate manner. The investigator must immediately notify BMS of this event and record the pregnancy on the Pregnancy Surveillance Form (not an SAE form). Initial information on a pregnancy must be reported immediately to BMS, and the outcome information provided once the outcome is known. Completed Pregnancy Surveillance Forms must be forwarded to BMS according to SAE reporting procedures.

Any pregnancy that occurs in a female partner of a male study participant should be reported to the sponsor. Information on this pregnancy will be collected on the Pregnancy Surveillance Form. Protocol-required procedures for study discontinuation and follow-up must be performed on the subject unless contraindicated by pregnancy (e.g., x-ray studies). Other appropriate pregnancy follow-up procedures should be considered if indicated. In addition, the investigator must report to BMS, and follow-up on information regarding the course of the pregnancy, including perinatal and neonatal outcome. Infants should be followed for a minimum of 8 weeks.

12.0 STATISTICAL CONSIDERATIONS

Sample size justification

Though not a standard endpoint for a phase II trial, the current study will utilize 1 year overall survival as the primary endpoint. Given that late responses (and variable response patterns such as responses after documented progression) have occurred in patients with other solid tumors treated with ipilimumab, and given that the use of the irRC and timing of the scans in our study will bias progression-free survival endpoints, overall survival will provide the most definitive endpoint to consider the activity of the current regimen in the context of historical controls. The 1 year overall survival of patients treated with cisplatin and gemcitabine alone is approximately 60%³.

The primary objective is to estimate the 1 year overall survival (OS) rates for gemcitabine, cisplatin, plus ipilimumab. The sample size is based on 90% one-sided confidence intervals (CI) calculated at the target rate of 80% for 1 year OS. We will recommend the regimen if lower bound of the resulting CI exceeds 60%. This is equivalent to testing the following hypothesis at Type I error level 0.10: H_0 : 1-year overall survival rate $\leq 60\%$, vs. H_a : 1-year overall survival rate $> 60\%$. To calculate the sample size, we derive an

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upper bound for the Greenwood formula for the variance of Kaplan-Meier estimate at 1 year. The upper bound is derived by assuming that all patients will be followed for at least 1 year from the enrollment. We expect an accrual rate of approximately 1-2 per month. This leads to approximately 17-34 months for accrual. With at least one year follow-up for the last subject, we expect the study to finish within approximately 2.5-3 years. The upper bound is obtained by maximizing over all possible censoring distributions. The resulting sample size is 33 in order to obtain a power level of 0.80. To account for potential missing data due to various reasons, we inflate by 10% and enroll 36 subjects. .

The analysis population will be the group who receives at least one cycle of protocol therapy. Therefore subjects who experience clinical deterioration and are removed from the study prior to cycle 3 (the first cycle with ipilimumab) will still be included in the analysis; however, based on prior studies of first-line therapy in patients with metastatic urothelial cancer, we expect this population to be very small. {Hahn, 2011 #1449} The starting point for survival analysis is the treatment (Gem+Cis) initiation date.

Statistical Analysis

Primary Objective:

- To determine the 1-year overall survival of patients with advanced/metastatic urothelial cancer treated with gemcitabine, cisplatin, plus ipilimumab.

The confidence interval of 1 year overall survival (OS) rates will be constructed based on Kaplan-Meier estimate.

Secondary Objectives:

- To determine the progression-free survival (using irRC) of patients with advanced/metastatic urothelial carcinoma treated with gemcitabine, cisplatin, and ipilimumab.

Progression-free survival will be analyzed using KM technique and the Cox regression model for exploring association with covariates.

- To determine the disease control rate (complete response + partial response + stable disease using irRC and RECIST v1.0 [see Section 8.2]) to treatment with gemcitabine, cisplatin, plus ipilimumab.

Response rates will be analyzed using statistical methods for binary outcomes.

- To determine the safety of treatment with gemcitabine, cisplatin, plus ipilimumab.

Association between immune-related adverse events and overall response rate will be tested using Fisher's exact test and Chi-square test.

Exploratory Objectives:

Please refer the correlative science plan for the detailed statistical analysis (Attachment). Potential biomarkers will be assessed by repeating the analysis of each clinical outcome with the level of each individual marker included as factor or covariate as appropriate. We will correlate outcomes with changes in the frequency of circulating immune cells, tumor antigen-specific CD8+ T cells, and whole blood

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transcriptional profiling before and after treatment. Significance of this association will be evaluated using the Chi-square test for binary outcomes and log-rank tests for time-to-event outcomes.

Stopping rule

After the first three enrolled patients have completed at least 1 cycle of combination therapy, accrual will be held allowing a safety review. The decision to proceed with enrollment will be based on a discussion among the principal investigator, co-investigators, and study statistician regarding the frequency and severity of adverse events. In addition, an early stopping rule will be employed. If we are confident that more than 20% of patients have experienced a nondermatologic immune-related adverse event of grade 3 or higher attributable to ipilimumab, that cannot be alleviated or controlled by appropriate care or corticosteroid therapy within 14 days after the initiation of supportive care or corticosteroid therapy, the study will close to further enrollment. We will therefore monitor the study when 5, 10, 20, and 30 patients have completed 6 cycles of treatment. We will continue enrollment while the toxicity evaluation is taking place (we will not halt enrollment for the analysis). The study regimen will be considered excessively toxic if we observe 3 or more out of 5, 4 or more out of 10, 6 or more out of 20, and 9 or more out of 30 patients. We will then stop the trial. These boundaries are determined from the lower bound of 80% exact binomial confidence intervals.

For true toxicity rate as 0.05, 0.10, 0.20, 0.30, 0.40 and 0.50, the probabilities of stopping the trial due to toxicity monitoring before/at $n = 5, 10, 20$ and 30 are referenced in Table 10 below.

Table 10: Probabilities of stopping the trial due to toxicity monitoring rule

True toxicity rate	N=5	N=10	N=20	N=30
0.05	0.0012	0.0022	0.0025	0.0025
0.10	0.0086	0.0212	0.0323	0.0342
0.20	0.0579	0.1718	0.3339	0.4196
0.30	0.1631	0.4563	0.7736	0.9023
0.40	0.3174	0.7391	0.9672	0.9969
0.50	0.5000	0.9141	0.9982	1.0000

13.0 TRIAL MANAGEMENT

13.1 Quality Controls and Quality Assurance:

13.1.1 Study Monitoring

Monitoring visits to the trial sites will be made periodically during the trial, to ensure all aspects of the protocol are followed. Source documents will be reviewed for verification of agreement with data as submitted via the data collection system. The investigator/institution guarantee access to source documents by HCRN or its designee and appropriate regulatory agencies.

The trial site may also be subject to quality assurance audit by BMS or its designee as well as inspection by appropriate regulatory agencies.

It is important for the investigator and their relevant personnel to be available during the monitoring visits and possible audits and for sufficient time to be devoted to the process.

13.1.2 Data and Safety Monitoring Plan

HCRN data safety monitoring activities include:

- Review of clinical trial conducted for progress and safety
- Review of all adverse events requiring expedited reporting as defined in the protocol
- Review of reports generated by data quality control review process
- Notification of the Sponsor Investigator of recommended action
- Notification of sites coordinated by the HCRN of adverse events requiring expedited reporting and subsequent committee recommendations for study modifications

13.1.3 Data/Safety Monitoring and Reporting Guidelines

HCRN will compile data summary reports for this trial and submit these reports monthly to the Sponsor-investigator. HCRN will submit data summary reports a minimum of twice a year to a Data Safety Monitoring Committee (DSMC) for review.

13.2 Data Handling and Record Keeping:

13.2.1 Case Report Forms

An electronic case report form (eCRF) is required and must be completed for each included patient. The completed dataset is the sole property of HCRN and should not be made available in any form to third parties, except for authorized representatives of appropriate Health/Regulatory Authorities, without written permission from HCRN.

13.2.2 Record Retention

To enable evaluations and/or audits from Health Authorities/HCRN, the investigator agrees to keep records, including the identity of all participating patients (sufficient information to link records; e.g., hospital records), all original signed informed consent forms, copies of all source documents, and detailed records of drug disposition. To comply with international regulations, the records should be retained by the investigator in compliance with regulations.

During data entry, range and missing data checks will be performed on-line. The checks to be performed will be documented in the Data Monitoring Plan for the study. A summary report (QC Report) of these checks together with any queries resulting from manual review of the eCRFs will be generated for each site and transmitted to the site and the site monitor. Corrections will be made by the study site personnel. This will be done on an ongoing basis.

13.3 Changes to the Protocol:

Study procedures will not be changed without the mutual agreement of the Sponsor Investigator, Hoosier Cancer Research Network, and BMS.

If it is necessary for the study protocol to be amended, the amendment or a new version of the study protocol (amended protocol) will be generated by the Hoosier Cancer Research Network and must be approved by each IRB, BMS, and if applicable, also the local regulatory authority. Local requirements must be followed.

If a protocol amendment requires a change to the Written Informed Consent Form, then the IRB must be notified. Approval of the revised Written Informed Consent Form by the IRB is required before the revised form is used.

The principal investigator is responsible for the distribution of these documents to his or her IRB, and to the staff at his or her center. The distribution of these documents to the regulatory authority will be handled according to local practice.

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BMS's willingness to supply study drug is predicated upon the review of the protocol. The Hoosier Cancer Research Network agrees to provide written notice to BMS of any modifications to the protocol or informed consent.

13.4 Ethics:

13.4.1 Ethics Review

The final study protocol, including the final version of the Written Informed Consent Form, must be approved or given a favorable opinion in writing by an IRB. The investigator must submit written approval to the HCRN office before he or she can enroll any patient into the study.

The principal investigator is responsible for informing the IRB of any amendment to the protocol in accordance with local requirements. In addition, the IRB must approve all advertising used to recruit patients for the study. The protocol must be re-approved by the IRB annually, as local regulations require.

Progress reports and notifications of serious unexpected adverse drug reactions will be provided to the IRB according to local regulations and guidelines.

The investigator is also responsible for providing the IRB with reports of any serious adverse drug reactions from any other study conducted with the investigational product. BMS will provide this information to the Sponsor Investigator. These reports will be reviewed by the Sponsor Investigator and those considered unexpected and possibly related to protocol therapy plus all deaths within 30 days of discontinuing treatment will be forwarded to participating sites for submission to their Institutional Review Boards per their guidelines. All other events will be held and submitted to the sites for continuing review.

13.4.2 Ethical Conduct of the Study

The study will be performed in accordance with ethical principles originating from the Declaration of Helsinki, which are consistent with ICH Good Clinical Practice, and applicable regulatory requirements.

13.5 Written Informed Consent:

The investigator will ensure the patient is given full and adequate oral and written information about the nature, purpose, possible risks and benefits of the study. Patients must also be notified they are free to discontinue from the study at any time. The patient should be given the opportunity to ask questions and allowed time to consider the information provided.

The patient's signed and dated informed consent must be obtained before conducting any procedure specifically for the study. The investigator must store the original, signed Written Informed Consent Form. A copy of the signed Written Informed Consent Form must be given to the patient.

Appendix A: Suggested Management of Immune-related Adverse Events

Inflammatory Events (immune-related Adverse Events or Immune-mediated Adverse Reactions)

Blocking CTLA-4 function may permit the emergence of autoreactive T cells and resultant clinical inflammatory AEs primarily involving the skin (dermatitis/pruritus), GI tract (diarrhea/colitis), liver (hepatitis), endocrine system (e.g. hypophysitis, adrenal and thyroid abnormalities) and other less frequent organs (e.g., uveitis/episcleritis). The majority of these inflammatory AEs manifested during treatment, however, a minority occurred weeks to months after stopping ipilimumab. The majority of the inflammatory AEs are reversible with the guidance issued below. In rare cases, these inflammatory AEs may be fatal.

Patients should be assessed for signs and symptoms of enterocolitis, dermatitis, neuropathy, and endocrinopathy, and clinical chemistries (including liver function and thyroid function tests) should be evaluated at baseline and before each dose of ipilimumab.

Efforts should be made to rule out neoplastic, infectious, metabolic, toxin or other etiologic causes prior to labeling an adverse event as suspected inflammatory AE. Serological, immunological, and histological data should be used to support the diagnosis of an immune-mediated toxicity.

Based on the current clinical experience with the use of corticosteroids for the management of treatment-emergent inflammatory AEs, corticosteroids do not adversely affect the antitumor response in subjects with objective responses and concomitant serious inflammatory AEs, such as Grade 3 colitis, requiring corticosteroid treatment. In other words, disease control was maintained without relapse or progression despite corticosteroid administration for the treatment of ipilimumab-related inflammatory AEs.

Gastrointestinal Toxicities

The lower GI tract was the most common site for ipilimumab-induced GI toxicity. Diarrhea due to treatment with ipilimumab ranged from mild to very severe with bloody stools. In some cases, diarrhea began as mild and then became severe colitis that was considered life threatening. Ipilimumab treatment may increase the possibility of GI perforation for those subjects who may receive high dose IL-2 following ipilimumab treatment. Constipation was rarely associated with ipilimumab administration. Delay in corticosteroid treatment may be associated with a poor outcome for subjects with high-grade diarrhea.

Liver Toxicities

Patients receiving ipilimumab may develop elevations in liver function tests (LFTs) in the absence of clinical symptoms. Occasionally, patients may present with symptoms including right upper quadrant abdominal pain or unexplained vomiting. Most of inflammatory hepatitis responded to high-dose corticosteroids (IV route recommended).

All patients require close medical monitoring of LFTs and immediate intervention to prevent serious sequelae. LFTs should be routinely assessed and reviewed prior to administration of each dose of ipilimumab.

Endocrine Toxicities

The most common inflammatory endocrine toxicities occurring in ipilimumab-treated patients are hypophysitis and hypopituitarism. Secondary cortisol deficiency (hypoadrenalism), hypothyroidism or thyroiditis and; and, less commonly, other endocrinopathies may occur concomitantly with hypophysitis; however these may also present as the only or as primary endocrinopathy. Most patients with hypopituitarism presented with nonspecific complaints such as fatigue, visual field defects, confusion, or impotence. Some patients have had headache as the predominant presentation. The majority of subjects with hypopituitarism demonstrated enlarged pituitary glands based on brain magnetic resonance imaging (MRI). Low adrenocorticotrophic hormone (ACTH) and cortisol were the most common biochemical abnormality; abnormal (mostly low) thyroid stimulating hormone (TSH), free T4, T3, testosterone or prolactin have also been reported in some subjects. Symptoms of hypopituitarism and other endocrine toxicities were generally controlled with appropriate hormone replacement.

Dermatologic Toxicities

Rash and pruritus was among the most common inflammatory AE; however, most cases were mild to moderate in severity. Two cases of fatal toxic epidermal necrolysis (TEN), considered drug-related, have been reported in clinical trials (ipilimumab and comparator/placebo).

Neurological Toxicities

Neurological manifestations in patients treated with ipilimumab may include motor and/or sensory neuropathy. Given the difficulty in definitely establishing an inflammatory etiology, alternative etiologies (e.g., tumor progression) should be excluded. Fatal Guillain-Barré syndrome and cases of myasthenia gravis have been reported in clinical trials of ipilimumab (Section 5.6.7.3). Unexplained motor neuropathy, muscle weakness, or sensory neuropathy should be evaluated and non-inflammatory causes such as disease progression, infections, metabolic disorders, and medications should be excluded.

Other Toxicities

Ocular inflammation, manifested as Grade 2 or Grade 3 episcleritis or uveitis, was associated with concomitant diarrhea in a few subjects (< 1%) and occasionally occurred in the absence of clinically apparent GI symptoms. Other presumed inflammatory AEs reported include, but were not limited to, arthritis/arthralgias, pneumonitis, pancreatitis, autoimmune (aseptic) meningitis, autoimmune nephritis, pure red cell aplasia, non-infective myocarditis, polymyositis, eosinophilia, pericarditis, urticaria (2%), large intestinal ulcer, esophagitis, acute respiratory distress syndrome, renal failure, infusion reactions, and myasthenia gravis, of which were individually reported for < 1% of subjects unless otherwise noted.

Suggested Evaluation and Treatment for Inflammatory Events

Early diagnosis and treatment intervention for inflammatory events can help prevent the occurrence of complications, such as GI perforation. Gastrointestinal (diarrhea and colitis) and skin (rash and pruritus)-related toxicities are the most common inflammatory events reported in studies with ipilimumab. Suggested evaluation procedures for suspected GI tract, liver, skin, endocrine, neurological and ocular toxicities are described below.

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Patients should be assessed for signs and symptoms of enterocolitis, dermatitis, neuropathy, and endocrinopathy, and clinical chemistries (including liver function and thyroid function tests) should be evaluated at baseline and before each dose of ipilimumab.

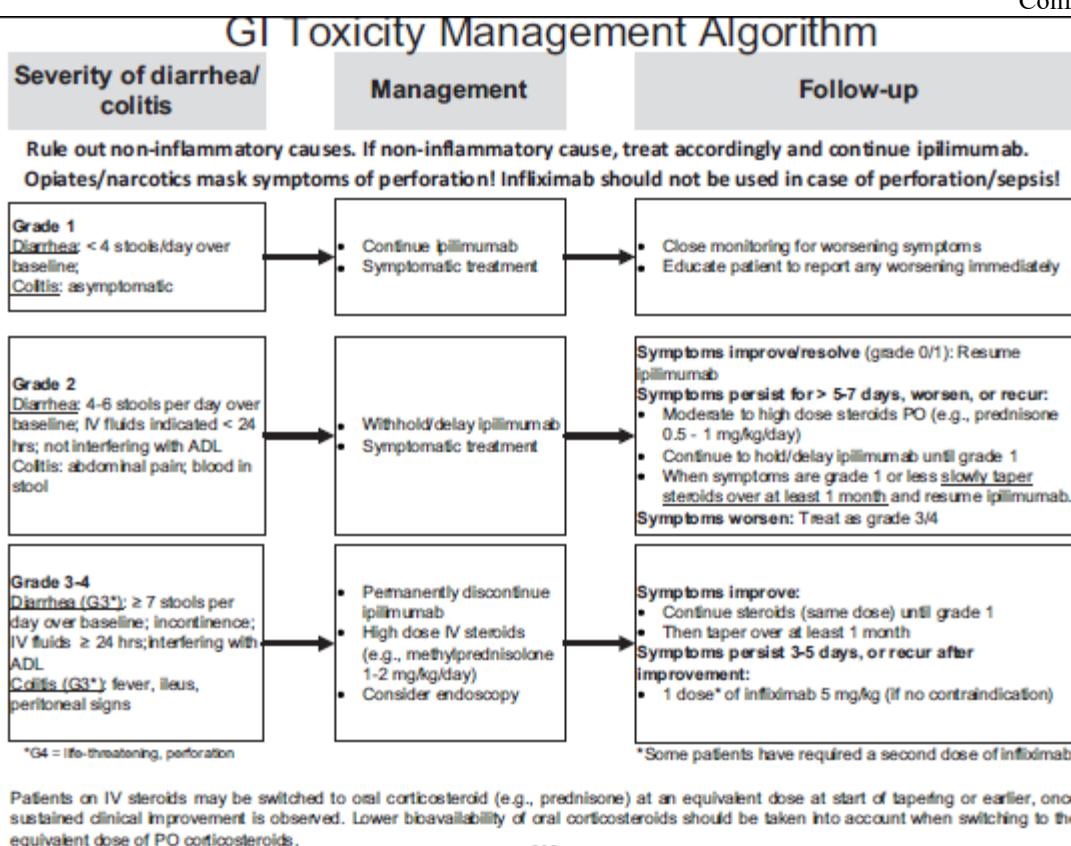
During evaluation of a suspected immune-mediated AE, all efforts should be made to rule out neoplastic, infectious, metabolic, toxic or other etiologic causes. Serological, immunological, imaging, and biopsy with histology (e.g., biopsy-proven lymphocytic) data should be used to support the diagnosis of an immune-mediated toxicity or support an alternative cause of the adverse event.

In general, for severe immune-mediated AEs, ipilimumab should be permanently discontinued and systematic high-dose corticosteroid therapy should be initiated. For moderate immune-mediated AEs, ipilimumab should be held or delayed and moderate dose corticosteroids should be considered. Upon improvement, corticosteroids should be tapered gradually over at least 1 month.

Gastrointestinal Tract

The differential diagnosis for subjects presenting with abdominal pain should include colitis, perforation, or pancreatitis. Additionally, a few subjects with abdominal pain also had acute swelling of the cecal wall on CT scan that may have represented localized inflammation.

Diarrhea (defined as either first watery stool, or increase in frequency 50% above baseline with urgency or nocturnal bowel movement, or bloody stool) should be further evaluated and infectious or alternate etiologies ruled out. Subjects should be advised to inform the investigator if any diarrhea occurs, even if it is mild. An algorithm for managing subjects with diarrhea or suspected colitis is provided in the figure below.



The majority of subjects with ipilimumab-induced diarrhea or colitis responded to symptomatic therapy or corticosteroids. Prednisone (for oral administration) or methylprednisolone (for IV administration) are recommended corticosteroids of choice for colitis. Caution should be taken in the use of narcotics in patients with abdominal pain or colitis/diarrhea as narcotic use may mask the signs of colonic perforation.

Permanent discontinuation of ipilimumab and starting high dose corticosteroid therapy (e.g., methylprednisolone 1-2 mg/kg/day IV or equivalent) is required for ipilimumab related \geq Grade 3 diarrhea/colitis. Upon improvement to grade 1 or less, corticosteroids should be slowly tapered according to symptomatic response over at least 1 month. Rapid corticosteroid tapering resulted in recurrence or worsening symptoms of enterocolitis, including perforation in some patients.

Patients on IV steroids may be switched to oral corticosteroids (e.g., prednisone) at an equivalent dose and start tapering earlier.

For subjects with ipilimumab-related Grade 2 diarrhea/colitis, ipilimumab should be held or delayed (as per protocol). Patients may be initially treated conservatively (e.g., with loperamide, fluid replacement). If symptoms persist for 5-7 days, worsen or recur, patients should be immediately switched to moderate to high dose corticosteroids (e.g., 0.5 - 1 mg/kg prednisone orally or equivalent). Most subjects with diarrhea/colitis will rapidly respond to initiation of corticosteroids. Upon improvement to grade 1 or less, the dose should be gradually tapered over at least 1-month. Treatment with ipilimumab may resume once the symptoms have improved to grade 1 or less.

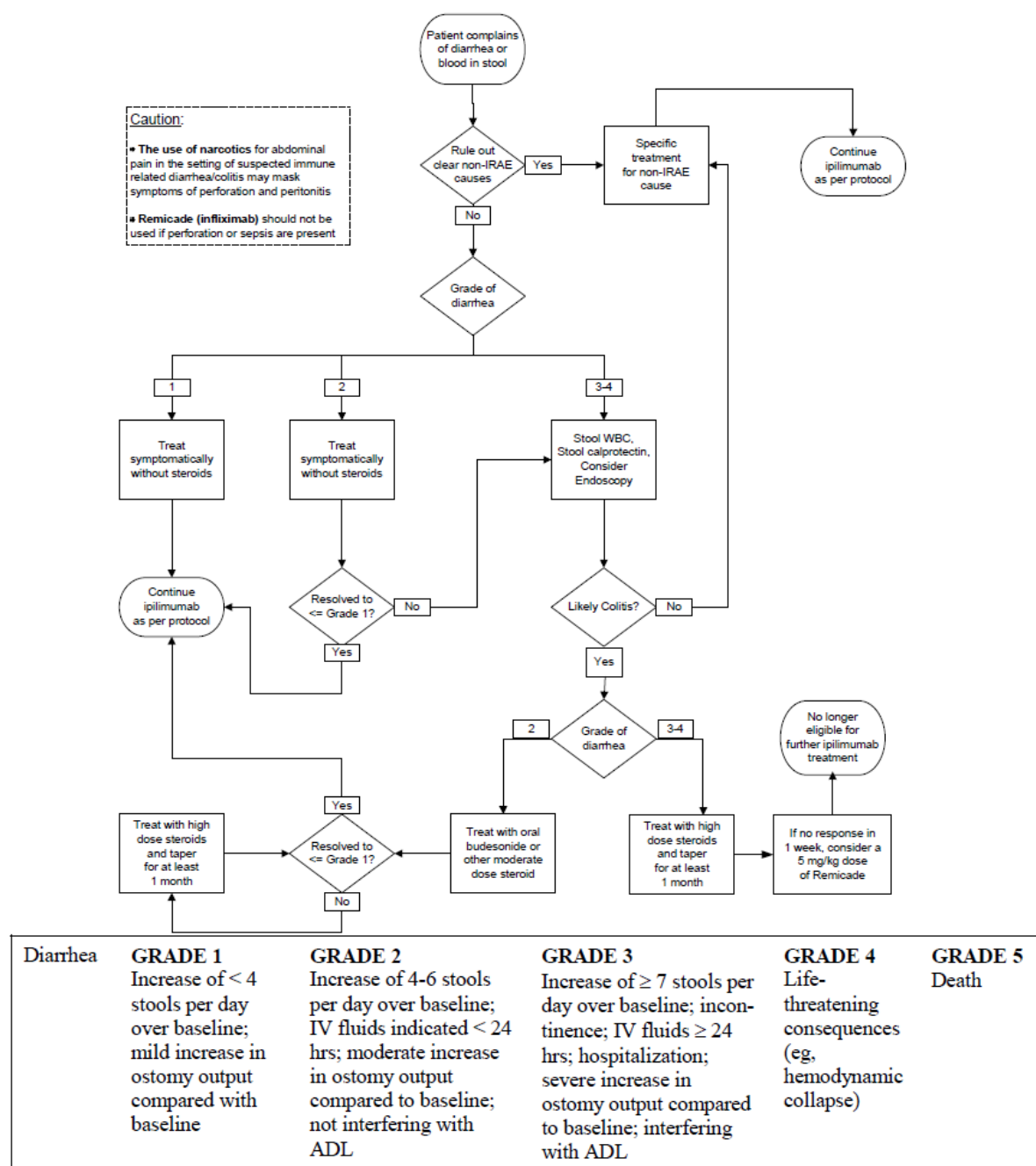
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Infrequently, subjects will appear refractory to corticosteroids or will flare following taper of corticosteroids. In these subjects, unless contraindicated (i.e., sepsis, perforation and other serious infections), a single dose of infliximab at 5 mg/kg may provide benefit. Some patients have required a subsequent additional dose of 5 mg/kg infliximab, although experience is limited.

For patients with concomitant immune related hepatitis, use of mycophenolate mofetil (MMF) is recommended in place of infliximab. For patients with long-term immunosuppressive therapy, administer antimicrobial prophylactics as appropriate per institutional guidelines. Such cases should be discussed with the Principal Investigator.

If the event is prolonged or severe or is associated with signs of systemic inflammation or acute phase reactants (e.g., increased CRP or platelet count; or bacteremia), it is recommended that sigmoidoscopy (or colonoscopy, if appropriate) with colonic biopsy of 3 to 5 specimens for standard paraffin block be performed. If possible, 1 to 2 biopsy specimens should be snap-frozen and stored. All subjects with confirmed colitis should also have an ophthalmologic examination, including a slit-lamp exam, to rule out uveitis. Tests should also be performed for stool calprotectin and WBCs as outlined below.

Diarrhea Management Algorithm



Liver

Liver function tests should always be performed and reviewed prior to administration of all ipilimumab doses. Patients treated with ipilimumab may develop elevation in LFT in the absence of clinical symptoms. In addition, subjects presenting with right upper quadrant abdominal pain, unexplained nausea, or vomiting should have LFTs performed immediately and reviewed before administering the next dose of study drug.

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Any increase in LFT should be evaluated to rule out non-inflammatory causes of hepatotoxicity including infections, disease progression or medications and followed with frequent LFT monitoring at 3-day intervals until resolution. An ANA, perinuclear antineutrophil cytoplasmic antibody (pANCA), and anti-smooth muscle antibody test may be performed if an autoimmune etiology is considered although these have been negative in some patients with inflammatory hepatitis due to ipilimumab.

Patients with Grade 2 AST or ALT or total bilirubin elevations (AST/ALT > 2.5 x ULN, total bilirubin [Tbili] > 1.5 x ULN) should be followed with frequent LFT monitoring at 3-day intervals until resolution or return to baseline. Delay or withhold ipilimumab while investigating alternative etiologies (e.g. tumor progression, infectious causes, medication). If elevations persist for more than 5 to 7 days or worsen and no alternative etiologies are identified, consider moderate to high dose corticosteroids (e.g., 0.5 to 1 mg/kg/day prednisone orally or equivalent). Upon improvement to Grade 1 or less, corticosteroids should be tapered over at least 1 month, and treatment with ipilimumab may resume.

Grade 3-4 hepatitis: For patients with Grade 3-4 AST or ALT or total bilirubin elevations (AST/ALT > 5.0 x ULN, Tbili > 3.0 x ULN), ipilimumab should be

- held or delayed (LFTs \leq 8 x ULN and Tbili \leq 5 x ULN)
- discontinued (LFTs > 8 x ULN, or Tbili > 5 x ULN)

Systemic IV high dose corticosteroids (e.g., 1 to 2 mg/kg/day methylprednisolone or equivalent) should be administered. For grade 4 events, the recommended dose of methylprednisolone is 2 mg/kg/day IV. Consultation with a hepatologist or gastroenterologist is recommended.

Once the LFT and Tbili improve to Grade 2:

- Corticosteroids should be slowly taper over at least 1 month.
- Treatment with ipilimumab may resume once patient meets protocol specific retreatment criteria, unless ipilimumab was previously discontinued

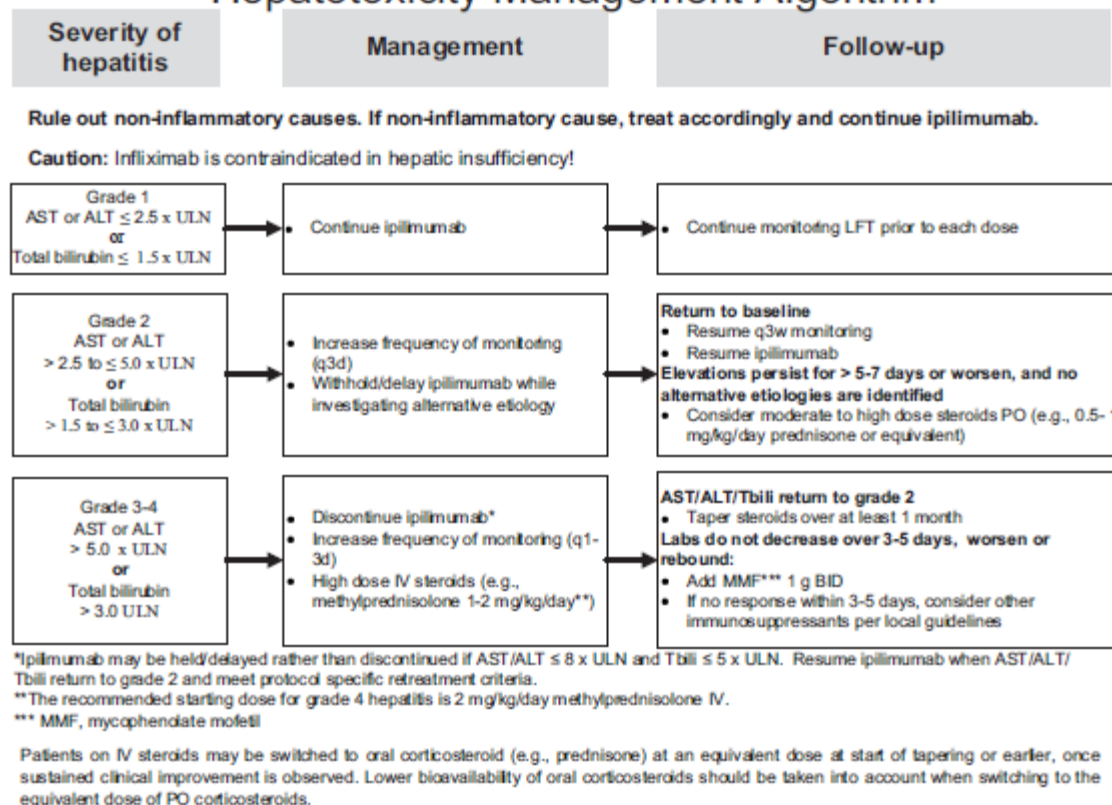
Patients on IV steroids may be switched to oral corticosteroid (e.g., prednisone) at an equivalent dose and start tapering or earlier.

Liver toxicity refractory to corticosteroids: In patients whose LFTs worsen, or do not decrease with corticosteroid therapy within 3 to 5 days or who have an LFT flare during corticosteroid tapering that is not responsive to an increase in corticosteroids, consultation with gastroenterologist/hepatologist and addition of immunosuppression with MMF 1 g PO BID per institutional guidelines should be considered. For patients not responding to mycophenolate mofetil within 3-5 days, contact the medical monitor. Additional immunosuppression per institutional guidelines for autoimmune hepatitis /liver transplant may be considered.

Patients receiving immunosuppression for more than 4 weeks should be evaluated for prophylaxis of opportunistic infections per institutional guidelines.

An algorithm for management of hepatotoxicity is shown below.

Hepatotoxicity Management Algorithm



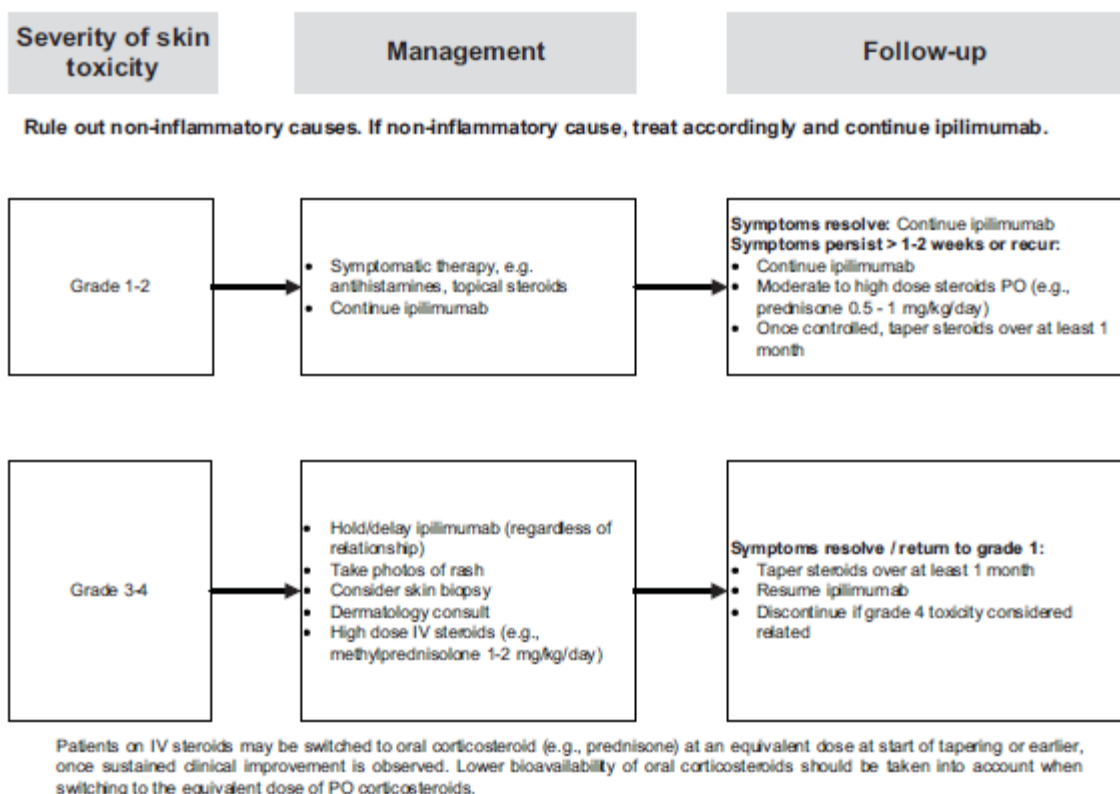
Skin

A dermatologist should evaluate persistent or severe rash or pruritus. A biopsy should be performed if appropriate and if possible, photos of the rash should also be obtained. Patients with low-grade ipilimumab-related skin toxicity (Grade 1 or 2) may remain on therapy and could be treated with symptomatic therapy (e.g., antihistamines). Low-grade symptoms persisting for 1 to 2 weeks and not responding to topical corticosteroid, moderate to high dose oral corticosteroid therapy should be initiated (e.g., prednisone 0.5 to 1 mg/kg once daily or equivalent). High-grade (Grade 3 or 4) symptoms require high-dose IV corticosteroid therapy (e.g., methylprednisolone 1 to 2 mg/kg/day or equivalent). A skin biopsy should be performed if possible. Once rash or pruritus is controlled to grade 2 or less, corticosteroids may be gradually tapered over a period of at least 1 month. Patients on IV steroids may be switched to oral corticosteroid (e.g., prednisone) at an equivalent dose and start tapering earlier.

Patients with any high-grade skin related toxicity (Grade 3 regardless of causality and grade 4 if unrelated) have to skip or delay ipilimumab (as per protocol) and may only continue treatment with ipilimumab if the initial symptoms have improved to \leq Grade 2. Patients with grade 4 skin toxicities considered to be related to ipilimumab have to permanently discontinue ipilimumab.

An algorithm for evaluating patients with skin toxicities is provided below:

Skin Toxicity Management Algorithm



Endocrine

Most subjects with hypopituitarism presented with nonspecific complaints such as fatigue, visual field defects, confusion, or impotence. Some have had headache as the predominant presentation. The majority of subjects with hypopituitarism demonstrated enlarged pituitary glands based on brain MRI. Low ACTH and cortisol were the most common biochemical abnormality; low TSH, free T4, T3, testosterone or prolactin have also been reported in some subjects. Subjects with unexplained symptoms such as fatigue, myalgias, impotence, mental status changes, or constipation should be investigated for the presence of thyroid, pituitary or adrenal endocrinopathies. An endocrinologist should be consulted if an endocrinopathy is suspected. If there are any signs of adrenal crisis such as severe dehydration, hypotension, or shock, intravenous corticosteroids with mineralocorticoid activity (e.g., methylprednisolone or equivalent) should be initiated immediately. If the patient's symptoms are suggestive of an endocrinopathy but the patient is not in adrenal crisis, an endocrine laboratory results should be evaluated before corticosteroid therapy is initiated.

Endocrine work up should include at least Thyroid stimulating hormone and free T4 levels should be obtained to determine if thyroid abnormalities are present. TSH, prolactin and a morning cortisol level will help to differentiate primary adrenal insufficiency from primary pituitary insufficiency. Radiographic imaging (e.g., MRI) with pituitary cuts should be performed.

In patients with clinically asymptomatic TSH abnormalities (TSH < 0.5 x LLN, or TSH > 2.0 x ULN, or TSH consistently out of range in two subsequent measurements at least 3 weeks apart), free T4 (fT4)

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should be measured at the next ipilimumab dosing. In primary pituitary endocrinopathy, fT4 abnormalities may lag behind TSH abnormalities.

Therefore:

- **If fT4 is normal**, fT4 measurements should be continued at each cycle until TSH returns to normal, or until endocrinology consult recommends no further testing.
- **If fT4 is abnormal**, an endocrinology consultation should be obtained to evaluate whether the patient requires substitution or other treatment. Ipilimumab dosing may be continued as long as the patient is asymptomatic.

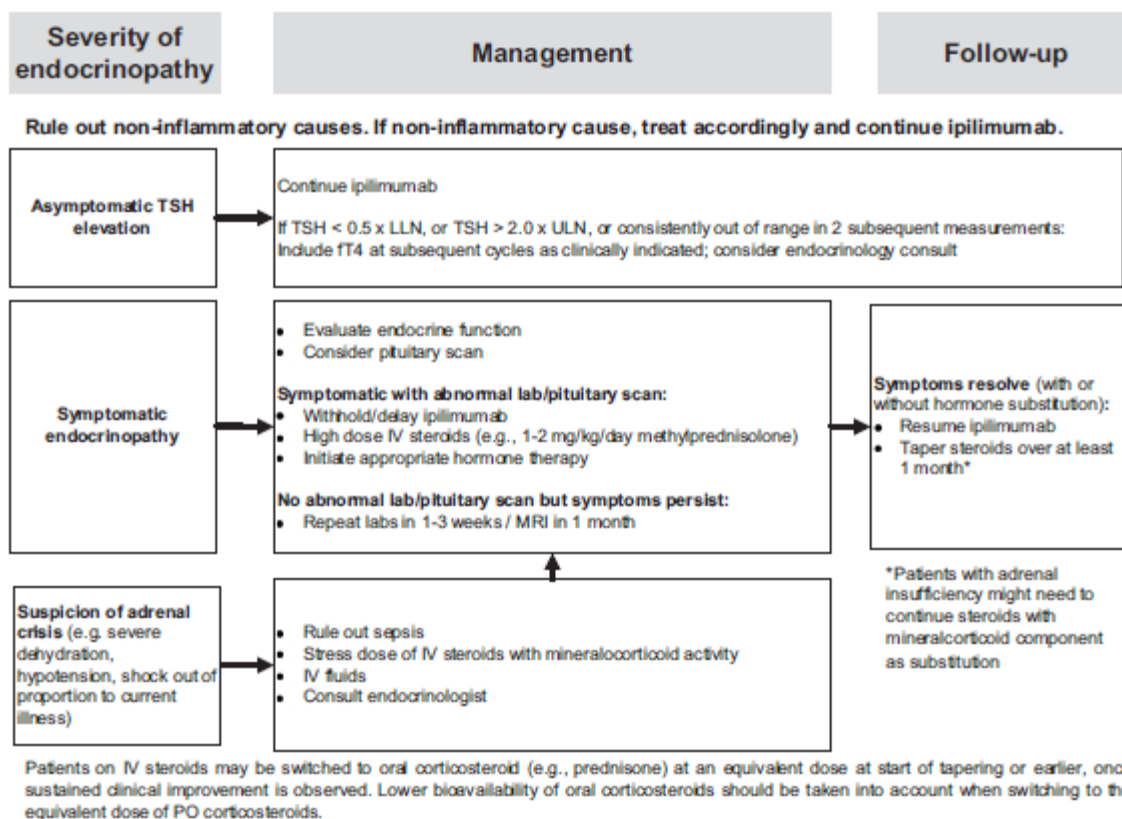
If the pituitary scan and/or endocrine laboratory tests are abnormal, hold or delay ipilimumab (per protocol) and a short course of high dose corticosteroids (e.g., 1 to 2 mg/kg/day prednisone or equivalent) should be considered in an attempt to treat the presumed pituitary inflammation, but it is currently unknown if this will stop or reverse the pituitary dysfunction. Abrupt discontinuation of corticosteroids should be avoided due to possible prolonged adrenal suppression. Once symptoms or laboratory abnormalities are controlled, and overall patient improvement is evident, patients on IV corticosteroids can be converted to the oral equivalent of prednisone and the corticosteroid tapered gradually over a period of at least 1 month.

Appropriate hormone replacement therapy should be instituted if an endocrinopathy is documented, and it is possible that subjects may require chronic hormone replacement.

Ipilimumab dosing may resume once symptoms are controlled (with or without hormone substitution).

An endocrinopathy management algorithm is presented below.

Endocrinopathy Management Algorithm



Neurological

Patients should be monitored for signs and symptoms of motor or sensory neuropathy or muscular symptoms. Subjects presenting with sensory symptoms lasting more than 4 days or motor symptoms confirmed by physical examinations should be evaluated and non-inflammatory causes such as disease progression, infections (including Lyme disease), metabolic syndromes and medications (such as taxanes and/or platinum salts) should be ruled out. A neurology consult should be obtained and diagnostic characterization of the neurological syndrome (electromyogram, nerve conduction studies) should be started.

The next dose of ipilimumab should be held or delayed (as per protocol) if the event of a Grade 2 neuropathy (sensitive or motor) is considered related to study drug. Treatment may resume upon improvement to grade 1 or less. The administration of ipilimumab should be permanently discontinued in patients with Grade 3 or 4 sensory neuropathy suspected to be related to study drug. Patients should be treated according to institutional guidelines and the administration of high dose IV corticosteroids (e.g., methylprednisolone 1 to 2 mg/kg per day or equivalent) should be considered.

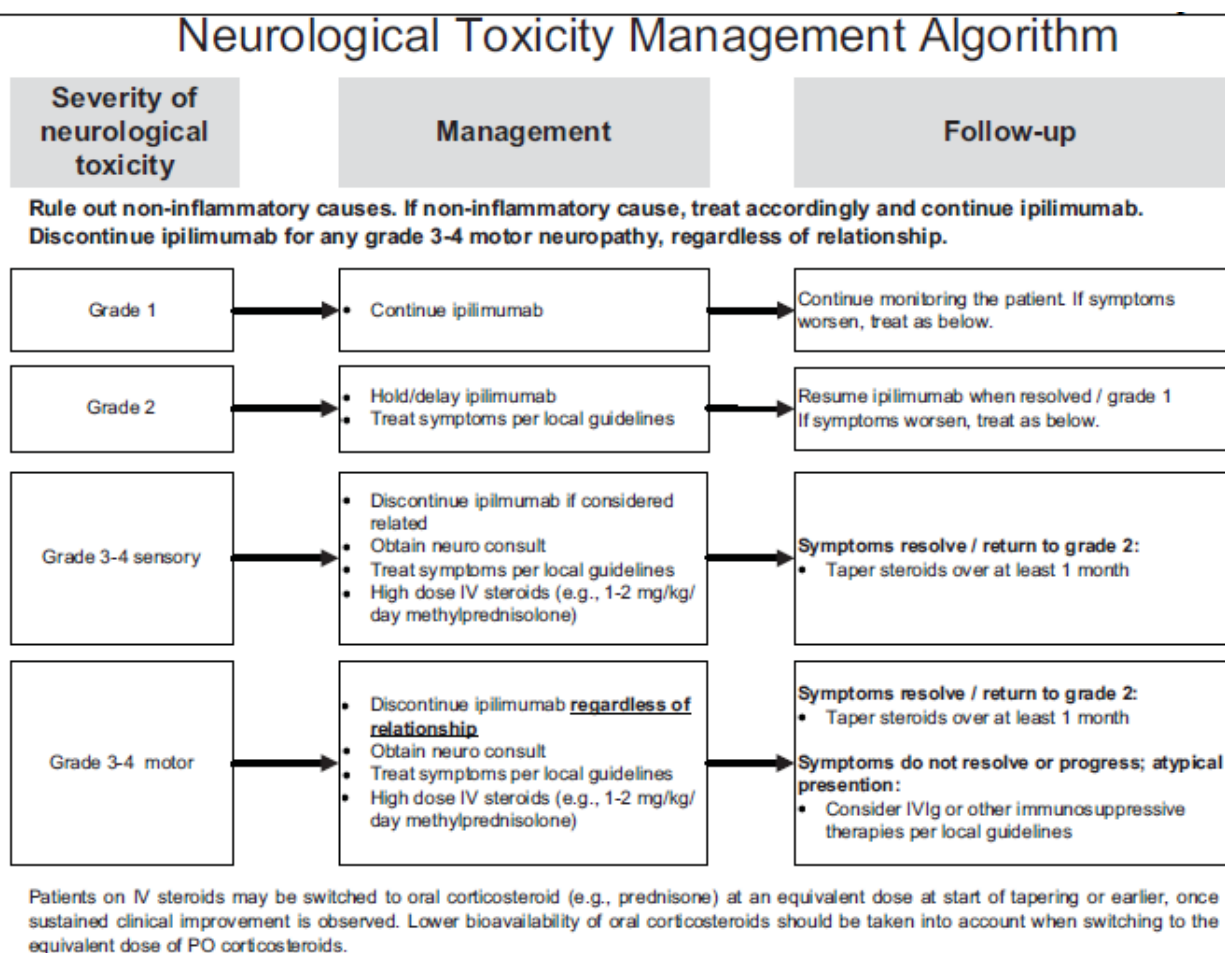
The administration of ipilimumab should be permanently discontinued in patients with Grade 3 or 4 motor neuropathy regardless of the causality to study drug. Patients with Grade 3 or 4 motor neuropathy who are clinically stable should be treated according to institution guidelines and the administration of high dose IV corticosteroids therapy (e.g., methylprednisolone 1 to 2 mg/kg per day or equivalent) should be considered.

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Patients with Grade 3 or 4 motor neuropathy who are not clinically stable or who have atypical symptoms should be hospitalized and high dose IV administration of corticosteroids should be initiated. Per clinical judgment, IV immunoglobulin (IV Ig) or other immunosuppressive therapies (as appropriate) should be considered.

When the symptoms improve to Grade 2, corticosteroids may be tapered over at least one month. Patients on IV steroids may be switched to oral corticosteroid (e.g., prednisone) at an equivalent dose and start tapering earlier.

A neuropathy management algorithm is presented below.



Other

Ocular inflammation (episcleritis or uveitis) was reported in a few subjects. These conditions responded to topical corticosteroid therapy. An ophthalmologist should evaluate visual complaints with examination of the conjunctiva, anterior and posterior chambers, and retina. Visual field testing and an electroretinogram should also be performed. Examination and testing should be documented on the appropriate case report form (CRF). Ipilimumab-related uveitis or episcleritis may be treated with topical corticosteroid eye drops.

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Symptoms of abdominal pain associated with elevations of amylase and lipase suggestive of pancreatitis may be associated with anti-CTLA-4 monoclonal antibody administration. The differential diagnosis of acute abdominal pain should include pancreatitis. Appropriate evaluation should include serum amylase and lipase tests.

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