Randomized phase 2 trial of gemcitabine + carboplatin + nivolumab versus gemcitabine + oxaliplatin + nivolumab in cisplatin-ineligible patients with metastatic urothelial cancer

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Trial Supported by
Bristol-Myers Squibb Company
BMS # CA209-9GC

Investigational New Drug (IND) # 135842

Initial Protocol Version Date: 12JUL2017 revised
Protocol Amendment Version Date:
13FEB2018 (LEAD SITE ONLY)
28MAR2018 (PARTICIPATING SITES ONLY)
05FEB2019
30DEC2019
29DEC2020
12AUG2021

PROTOCOL SIGNATURE PAGE

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VERSION DATE: 12AUG2021

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, 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 institutional review board(s).

_____ _____

Signature of Site Investigator Date

_____

Site Investigator Name (printed)

_____

Site Investigator Title

_____

Name of Facility

_____

Location of Facility (City and State)

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SYNOPSIS

TITLE	Randomized phase 2 trial of gemcitabine + carboplatin + nivolumab versus gemcitabine + oxaliplatin + nivolumab in cisplatin-ineligible patients with metastatic urothelial cancer
PHASE	II
OBJECTIVES	**Primary Objective** Estimate the objective response rate (RECIST 1.1) to treatment with gemcitabine + carboplatin + nivolumab and gemcitabine + oxaliplatin + nivolumab in cisplatin-ineligible patients with metastatic urothelial cancer. **Secondary Objectives** • Determine the safety of gemcitabine + carboplatin + nivolumab and gemcitabine + oxaliplatin + nivolumab in cisplatin-ineligible patients with metastatic urothelial cancer (CTCAE v4) • Estimate the duration of response to treatment with gemcitabine + carboplatin + nivolumab and gemcitabine + oxaliplatin + nivolumab in cisplatin-ineligible patients with metastatic urothelial cancer • Estimate the progression-free survival • Estimate the overall survival. **Exploratory Objectives** • Explore the effects of treatment on peripheral blood biomarkers of immune modulation and immunogenic cell death. • Explore the impact of genomic/genetic alterations, including DNA damage response gene alterations, on clinical outcomes. • Explore the tumor immune microenvironment including the composition and frequency of immune cells and expression of immune checkpoints in archival tumor tissue and the relationship with clinical outcomes.
STUDY DESIGN	This is a randomized phase 2 trial of gemcitabine + carboplatin + nivolumab or gemcitabine + oxaliplatin + nivolumab for the treatment of cisplatin-ineligible patients with metastatic urothelial cancer. Randomization will be stratified on the lymph node only (and/or unresectable primary) metastatic status.

ELIGIBILITY CRITERIA (See Section 3 for full eligibility)	**Inclusion Criteria** 1. Written informed consent and HIPAA authorization for release of personal health information prior to registration. **NOTE:** HIPAA authorization may be included in the informed consent or obtained separately. 2. Age ≥ 18 years at the time of consent. 3. Eastern Cooperative Oncology Group (ECOG) performance status of ≤ 2. 4. Able to comply with the study protocol, in the investigator's judgment. 5. Histologically documented, locally advanced (T4b, any N; or any T, N 2−3) or metastatic urothelial carcinoma (mUC) (M1, Stage IV) (also termed TCC or UCC of the urinary tract; including renal pelvis, ureters, urinary bladder, and urethra) Patients with mixed histologies are required to have a dominant transitional cell pattern. Locally advanced bladder cancer must be inoperable on the basis of involvement of pelvic sidewall or adjacent viscera (clinical Stage T4b) or bulky nodal metastasis (N2−N3). 6. Measurable disease, as defined by RECIST v1.1. 7. Representative formalin-fixed paraffin-embedded (FFPE) tumor specimens in paraffin blocks (blocks preferred) or at least 15 unstained slides. If archival tissue is not available, enrollment will be considered on a case by case basis after discussion with the sponsor investigator. 8. No prior chemotherapy for inoperable locally advanced or mUC. For patients who received prior adjuvant/neoadjuvant chemotherapy or chemo-radiation for urothelial carcinoma, a treatment-free interval > 12 months between the last treatment administration and the date of recurrence is required in order to be considered treatment naive in the metastatic setting. 9. Cisplatin-ineligible as defined by at least one of the following[2]: • Calculated creatinine clearance ≥30 but ≤ 60 mL/min (Cockroft-Gault) • ECOG performance status = 2 • CTCAE v4 Grade ≥ 2 audiometric hearing loss

10. Demonstrate adequate organ function as defined in the table below. All screening labs to be obtained within 28 days prior to registration.

System	Laboratory Value
Hematological	
Absolute Neutrophil Count (ANC)	$\geq 1.5 \times 10^9$/L
Hemoglobin (Hgb)	≥ 9 g/dL
Platelets	$\geq 100 \times 10^9$/L
Renal	
Calculated creatinine clearance[1]	≥30 mL/min
Hepatic	
Bilirubin	≤ 1.5 × upper limit of normal (ULN) (except subjects with Gilbert Syndrome, who can have total bilirubin < 3.0 mg/dL)
Aspartate aminotransferase (AST)	≤ 3 × ULN
Alanine aminotransferase (ALT)	≤ 3 × ULN

[1] Cockcroft-Gault formula will be used to calculate creatinine clearance (See SPM)

11. Women of childbearing potential (WOCBP) and male subjects must use appropriate method(s) of contraception as outlined in Section 5.6.

12. Women of childbearing potential must have a negative serum or urine pregnancy.

Exclusion Criteria

1. Active infection requiring systemic therapy.

2. Pregnant or breastfeeding (**NOTE:** breast milk cannot be stored for future use while the mother is being treated on study).

3. Any serious or uncontrolled medical disorder that, in the opinion of the site investigator, may increase the risk associated with study participation or study drug administration, impair the ability of the subject to receive protocol therapy, or interfere with the interpretation of study results.

4. Prior malignancy active within the previous 3 years except for locally curable cancers that have been apparently cured.

5. Subjects with active, known or suspected autoimmune disease. Subjects with vitiligo, type I diabetes mellitus,

	residual hypothyroidism due to autoimmune condition only requiring hormone replacement, psoriasis not requiring systemic treatment, or conditions not expected to recur in the absence of an external trigger are permitted to enroll. 6. Subjects with a condition requiring systemic treatment with either corticosteroids (> 10 mg daily prednisone equivalents) or other immunosuppressive medications within 14 days of study drug administration. Inhaled or topical steroids and adrenal replacement doses > 10 mg daily prednisone equivalents are permitted in the absence of active autoimmune disease. 7. Prior treatment with an anti-PD-1, anti-PD-L1, anti-PD-L2, anti-CTLA-4 antibody, or any other antibody or drug specifically targeting T-cell co-stimulation or immune checkpoint pathways. 8. Grade ≥ 2 neuropathy (NCI CTCAE version 4). 9. Positive test for hepatitis B virus surface antigen (HBV sAg) or hepatitis C virus ribonucleic acid (RNA) or hepatitis C antibody (HCV antibody) indicating acute or chronic infection. 10. Known history of testing positive for human immunodeficiency virus (HIV) or known acquired immunodeficiency syndrome (AIDS). 11. Evidence of interstitial lung disease or active, non-infectious pneumonitis. 12. Significant cardiovascular disease, such as New York Heart Association cardiac disease (Class III or greater), myocardial infarction within 3 months prior to randomization, unstable arrhythmias, or unstable angina. 13. Known left ventricular ejection fraction (LVEF) < 40% Patients with known coronary artery disease, congestive heart failure not meeting the above criteria, or LVEF 40%−50% must be on a stable medical regimen that is optimized in the opinion of the treating physician, in consultation with a cardiologist if appropriate. 14. Solid organ or tissue transplant including stem cell transplant

STATISTICAL CONSIDERATIONS	A randomized, open-labeled phase 2 'pick a winner design' will be employed.[1] Two regimens are to be studied and the expected baseline response rate is ~40%. With 21 patients per arm, we have probability 0.9 of selecting the regimen that has a true response rate of 40%+20%=60% [or, allows selection of the regimen that is 18% better (in terms of response rate) than the other regimen with 0.88 probability and 15% better with 0.83probability]. We will inflate the sample size on each study arm to account for early drop-outs/unevaluable patients to 24 patients per arm.
TOTAL NUMBER OF SUBJECTS	N= 48
ESTIMATED ENROLLMENT PERIOD	Estimated 30 months
ESTIMATED STUDY DURATION	Estimated 48 months

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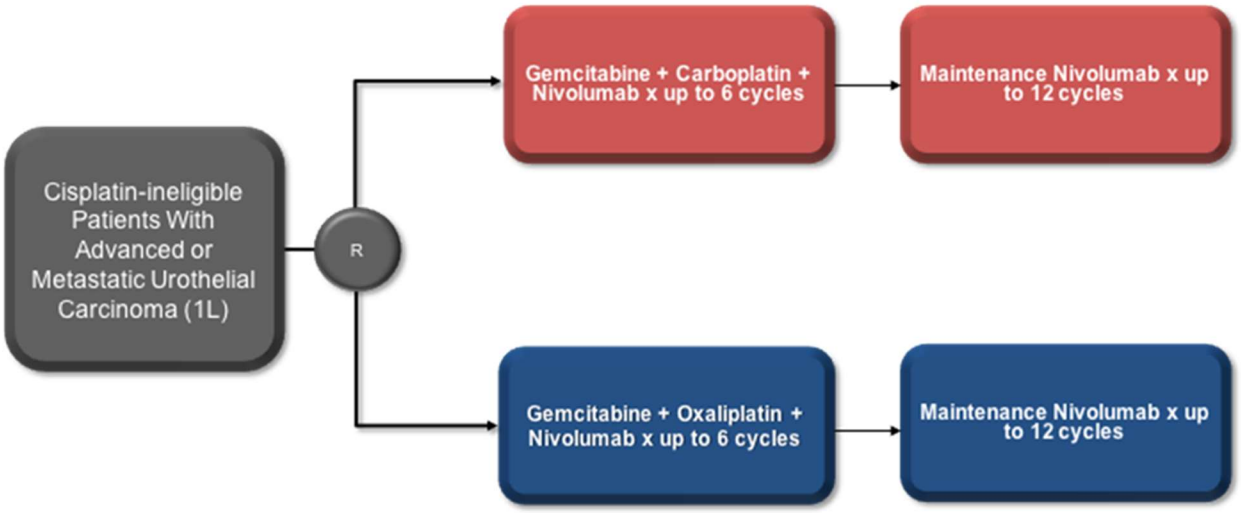
SCHEMA


Cisplatin-ineligible Patients With Advanced or Metastatic Urothelial Carcinoma (1L)
R
Gemcitabine + Carboplatin + Nivolumab x up to 6 cycles
Maintenance Nivolumab x up to 12 cycles
Gemcitabine + Oxaliplatin + Nivolumab x up to 6 cycles
Maintenance Nivolumab x up to 12 cycles

1. BACKGROUND AND RATIONALE

1.1 Standard treatment for cisplatin-ineligible patients with metastatic urothelial cancer

Cisplatin-based combination chemotherapy is standard first-line treatment for patients with metastatic urothelial cancer. However, a large proportion of patients with metastatic urothelial cancer are suboptimal candidates for such treatment due renal impairment and/or other smoking- and age-related comorbidities.[2–4] Carboplatin-based regimens, such as the doublet of gemcitabine plus carboplatin, have been substituted in cisplatin-ineligible patients but are associated with inferior efficacy.[5] Recently, single agent-PD-1 or PD-L1 inhibition as first-line treatment for cisplatin-ineligible patients with metastatic urothelial cancer has shown promise with encouraging safety and durable anticancer activity.[6] However, only ~20-25% of patients respond to treatment highlighting the need for combination regimens which extend these therapeutic benefits to a larger proportion of patients.[6]

1.2 Standard cytotoxic chemotherapy may induce immunogenic cell death

There is growing interest in regimens combining cytotoxic chemotherapy and immune checkpoint blockade.[7] The potentially favorable effects of chemotherapy on the antitumor immune response can be broadly grouped into two categories: (1) inducing immunogenic cell death and (2) disrupting strategies that tumors exploit to evade the immune response (e.g., modulating the quantity or function of immune cell subsets). Importantly, inducing immunogenic cell death may occur as part of the intended therapeutic effects of chemotherapy and therefore likely occurs at standard doses and schedules of chemotherapy (though based on data in model systems, is very much drug dependent). Alternatively, in model systems, various chemotherapeutic drugs can also deplete negative regulators of the immune response such as myeloid derived suppressor cells or regulatory T cells. Compared with the induction of immunogenic cell death, however, these effects of chemotherapy on the immune system are likely much more dose and schedule dependent (and may occur predominantly at unconventional doses and schedules). Despite a considerable literature on the impact of cytotoxic chemotherapy on the antitumor immune response, the vast majority of combination strategies being explored in the clinic to date simply combine cytotoxic drugs utilized for a particular disease indication with immune checkpoint blockade which may overlook the critical importance of the specific cytotoxic agents utilized. Optimizing combination strategies requires an understanding of the immunomodulatory effect of chemotherapy one is seeking to exploit and ideally demonstrating both clinical and pharmacodynamic evidence to support further study.

Immunogenic cell death refers to the process of cell death accompanied by release of tumor antigens along with the emission of danger-associated molecular patterns (DAMPs).[8,9] While normal apoptosis is non-immunogenic, and may even be tolerogenic, immunogenic cell death can induce an immune response through activation of dendritic cells and subsequently T cells. Immunogenic cell death occurs primarily as a result of endoplasmic reticulum stress and production of reactive oxygen species leading to translocation of DAMPs to the cell surface of the dying cell where it functions as an “eat me” signal. DAMPs involved in immunogenic cell death, including calreticulin and high-mobility group protein box-1 (HMGB1), bind to several pattern recognition receptors, such as Toll-like receptors (TLRs), which are expressed on antigen presenting cells. Importantly, genetic polymorphisms of the HMGB1-TLR4 axis have been shown to be associated with worse outcomes in patients with breast cancer and colon cancer

treated with chemotherapy underscoring the potential clinical relevance of immunogenic cell death.[10,11] Importantly, immunogenic cell death **requires all four events** to take place: (1) cell death, (2) calreticulin exposure, (3) ATP secretion and (4) HMGB1 release.

1.3 Oxaliplatin, but not cisplatin or carboplatin, induces immunogenic cell death in model systems

The platinum-based drugs cisplatin, carboplatin, and oxaliplatin are among the most widely used cytotoxics in oncology. Their main mechanism of action is believed to be the induction of cancer cell apoptosis as a response to covalent binding to DNA. However, the mechanistic basis for the anticancer effects of platinum drugs is likely much more complex based on studies indicating that cellular molecules other than DNA may potentially act as targets, and that the antitumor effects of platinum drugs may occur in part through immune modulation. **Importantly, cisplatin and carboplatin do not induce immunogenic cell death, despite their presumed identical mechanism of action to that of oxaliplatin.**[12,13] This is attributed to the lack of calreticulin exposure after cisplatin/carboplatin treatment as these compounds do induce ATP and HGMB-1 release. Indeed, the ability of drugs to trigger immunogenic cell death as a standalone intervention thereby converting dying cancer cells into a "vaccine" that is efficient in the absence of adjuvants is shared by a relatively restricted set of lethal triggers. **Among studies of triggers of immunogenic cell death in model systems to date, oxaliplatin has been consistently identified**.[12–14]

1.4 The doublet of gemcitabine plus oxaliplatin has shown safety and activity in cisplatin-ineligible patients with metastatic urothelial cancer

Though the doublet of gemcitabine plus carboplatin is generally considered standard therapy for cisplatin-ineligible patients with metastatic urothelial cancer, several phase 2 studies have explored the combination of gemcitabine plus oxaliplatin (Table 1) demonstrating both efficacy and safety in this patient population.

Table 1. Select Phase 2 Trials of Gemcitabine plus Oxaliplatin in Metastatic Urothelial Cancer

Authors	N	Cisplatin-ineligible?	Response Rate
Eroglu[15]	18	Majority	36%
Carles[16]	46	Yes	48%
Theodore[17]	30	Yes	47%

1.5 Nivolumab

Nivolumab (BMS-936558 or MDX1106) is a fully human monoclonal immunoglobulin (Ig) G4 antibody that binds to the programmed cell death receptor-1 (PD-1), a negative regulatory molecule expressed by activated T and B lymphocytes. Inhibition of the interaction between PD-1 and its ligands promote immune responses and antigen-specific T cell responses to both foreign and self antigens.

Nivolumab has demonstrated clinical activity as monotherapy, and as combination therapy in several tumor types including renal cell carcinoma, melanoma, non-small cell lung cancer, urothelial cancer, and some lymphomas. The majority of responses have been durable and

exceeded 6 months. The overall safety experience with nivolumab, as a monotherapy or in combination with other therapeutics, is based on experience in approximately 4,000 subjects treated to date. For nivolumab monotherapy, the safety profile has been similar across tumor types.

1.6 Nivolumab in urothelial cancer

The safety and activity of single-agent nivolumab in advanced urothelial cancer has been explored in two prospective clinical trials to date. CheckMate 032 was a phase 1/2 study enrolling 86 patients to treatment with nivolumab 3 mg/kg every 2 weeks; 78 received at least one dose of treatment.[18] A confirmed objective response was achieved in 19 (24.4%, 95% CI 15.3-35.4) of 78 patients and the vast majority of responses were durable. Based on these results, a large phase II trial was initiated to confirm the safety and activity of nivolumab in metastatic urothelial cancer. CheckMate 275 enrolled 270 patients with metastatic urothelial cancer who had progressed despite prior platinum-based chemotherapy.[19] With a minimum follow-up of 7 months, the objective response rate was 19.6% (95% CI 15.0-24.9%). While higher tumor PD-L1 expression (as measured by immunohistochemistry) on tumor cells was associated with a numerically higher objective response rate, responses were seen even in patients with PD-L1 expression <1% [objective response rate = 16.1% (95% CI 10.5–23.1]. Responses occurred rapidly [median time to response = 1.9 months (1.6–5.9)] and were durable; at a median follow-up of 7 months, 77% of responses were ongoing. The safety profile of nivolumab was consistent with what has been observed across other prior indications (Table 2 and 3).

Table 2. Treatment-related adverse events in ≥ 5% of patients (n=270)

Event	% Any Grade	%Grade 3–4
All treatment-related adverse events	64.4	17.8
Fatigue	16.7	1.9
Pruritus	9.3	0
Diarrhea	8.9	1.9
Decreased appetite	8.1	0
Hypothyroidism	7.8	0
Nausea	7.0	<1
Asthenia	5.9	1.5
Rash	5.9	1.1
Pyrexia	5.6	0
Treatment-related adverse events leading to discontinuation	4.8	3.0

Table 3. Immune mediated adverse events (n=270)

Events	%, Any Grade	%, Grade 3–4
Skin	17.4	1.5
Rash	5.9	1.1
Endocrine	14.4	<1
Hypothyroidism	7.8	0
Gastrointestinal	9.3	2.2
Diarrhea	8.9	1.9
Colitis	<1	<1
Pulmonary	4.1	1.1
Pneumonitis	3.7	<1
Hepatic	3.7	1.9
Elevated ALT enzymes	3.0	<1
Elevated AST enzymes	2.2	1.1
Renal	1.1	<1

1.7 Combining nivolumab with platinum-based chemotherapy

An expansion of the CheckMate 012 study explored nivolumab in combination with platinum-based chemotherapy in patients with advanced non-small cell lung cancer including combination regimens with gemcitabine plus cisplatin, paclitaxel plus carboplatin, or pemetrexed plus cisplatin (n= 56).[20] The safety profile of nivolumab plus platinum-based chemotherapy was consistent with that expected for the individual agents. A second trial explored the combination of nivolumab 10 mg/kg + gemcitabine plus cisplatin, pemetrexed plus cisplatin, paclitaxel plus carboplatin plus bevacizumab or docetaxel (n=24) in patients with advanced non-small cell lung cancer.[21] This trial demonstrated similar findings with no new safety signals observed with the combination regimens.

1.8 Rationale for current trial

This trial will test a straightforward, but as yet unexplored, hypothesis – that the choice of cytotoxic agents matters with regards to potential synergy when combining chemotherapy and immune checkpoint blockade. Specifically, we will test whether integration of a cytotoxic agent capable of inducing immunogenic cell death will improve outcomes in combination with PD-1 blockade.

In summary, the proposed trial is supported by the following lines of evidence:

1. The development of therapies for cisplatin-ineligible patients with metastatic urothelial cancer is an unmet need.
2. Single agent PD-1/PD-L1 blockade has shown durable responses in cisplatin-ineligible patients with metastatic urothelial cancer but only 20-25% of patients respond to treatment.
3. Chemotherapy has demonstrated immunomodulatory effects in model systems. In particular, induction of immunogenic cell death may lead to synergy in combination with immune checkpoint blockade. However, combination regimens have generally advanced to the clinic without consideration of the potential importance of the choice of cytotoxic agent.

4. Establishing proof-of-concept for the immunomodulatory effects of chemotherapy is likely best pursued in the chemotherapy-naïve setting (i.e., because achieving cell death is a prerequisite for achieving immunogenic cell death, chemotherapy naïve cancers will likely be most amenable).
5. Oxaliplatin has consistently been demonstrated to induce immunogenic cell death in model systems.
6. Gemcitabine plus oxaliplatin has already demonstrated safety and activity in multiple phase 2 trials in cisplatin-ineligible patients with metastatic urothelial cancer.

2. STUDY OBJECTIVES AND ENDPOINTS

2.1 Objectives

2.1.1 Primary Objective

- Estimate the objective response rate (RECIST 1.1) to treatment with gemcitabine + carboplatin + nivolumab and gemcitabine + oxaliplatin + nivolumab in cisplatin-ineligible patients with metastatic urothelial cancer.

2.1.2 Secondary Objectives

- Determine the safety of gemcitabine + carboplatin + nivolumab and gemcitabine + oxaliplatin + nivolumab in cisplatin-ineligible patients with metastatic urothelial cancer (CTCAE v4).
- Estimate the duration of response to treatment with gemcitabine + carboplatin + nivolumab and gemcitabine + oxaliplatin + nivolumab in cisplatin-ineligible patients with metastatic urothelial cancer.
- Estimate the progression-free survival
- Estimate the overall survival.

2.1.3 Correlative/Exploratory Objectives

- Explore the effects of treatment on peripheral blood biomarkers of immune modulation and immunogenic cell death
- Explore the impact of genomic/genetic alterations, including DNA damage response gene alterations, on clinical outcomes.
- Explore the tumor immune microenvironment including the composition and frequency of immune cells and expression of immune checkpoints in archival tumor tissue and the relationship with clinical outcomes.

2.2 Endpoints

2.2.1 Primary Endpoint

- Response rate as determined by RECIST v1.1

2.2.2 Secondary Endpoints

- Safety will be determined according to the NCI Common Terminology Criteria for Adverse Events (NCI CTCAE) v4

- Duration of response will be the time from the first documentation of RECIST 1.1 response to the time of progression as per RECIST 1.1.
- Progression-free survival which is defined as the time from randomization to death or progression, depending on which occurs first
- Overall survival is defined as the time from randomization to death

3. ELIGIBILITY CRITERIA

3.1 Inclusion Criteria

Subject must meet all the following applicable inclusion criteria to participate in this study:

1. Written informed consent and HIPAA authorization for release of personal health information prior to registration. **NOTE:** HIPAA authorization may be included in the informed consent or obtained separately.

2. Age ≥ 18 years at the time of consent.

3. Eastern Cooperative Oncology Group (ECOG) performance status of ≤ 2.

4. Able to comply with the study protocol, in the investigator's judgment.

5. Histologically documented, locally advanced (T4b, any N; or any T, N 2−3) or metastatic urothelial carcinoma (mUC) (M1, Stage IV) (also termed TCC or UCC of the urinary tract; including renal pelvis, ureters, urinary bladder, and urethra) Patients with mixed histologies are required to have a dominant transitional cell pattern. Locally advanced bladder cancer must be inoperable on the basis of involvement of pelvic sidewall or adjacent viscera (clinical Stage T4b) or bulky nodal metastasis (N2−N3).

6. Measurable disease, as defined by RECIST v1.1.

7. Representative formalin-fixed paraffin-embedded (FFPE) tumor specimens (metastatic specimens preferable but if not available primary tumor specimens that are at least muscle-invasive are acceptable) in paraffin blocks (blocks preferred) or at least 15 unstained slides. If archival tissue is not available, subjects may be considered for enrollment on a case by case basis after discussion with the sponsor-investigator.

8. No prior chemotherapy for inoperable locally advanced or mUC. For patients who received prior adjuvant/neoadjuvant chemotherapy or chemo-radiation for urothelial carcinoma, a treatment-free interval > 12 months between the last treatment administration and the date of recurrence is required in order to be considered treatment naive in the metastatic setting.

9. Cisplatin-ineligible as defined by at least one of the following[2]:
    - Calculated creatinine clearance ≥ 30 but ≤ 60 mL/min (Cockroft-Gault)
    - ECOG performance status = 2
    - CTCAE v4 Grade ≥ 2 audiometric hearing loss

10. Demonstrate adequate organ function as defined in the table below. All screening labs to be obtained within 28 days prior to registration.

System	Laboratory Value
Hematological	
Absolute Neutrophil Count (ANC)	$\geq 1.5 \times 10^9$/L
Hemoglobin (Hgb)	≥ 9 g/dL
Platelets	$\geq 100 \times 10^9$/L
Renal	
Calculated creatinine clearance[2]	≥ 30 mL/min
Hepatic	
Bilirubin	$\leq 1.5 \times$ upper limit of normal (ULN) (except subjects with Gilbert Syndrome, who can have total bilirubin < 3.0 mg/dL)
Aspartate aminotransferase (AST)	$\leq 3 \times$ ULN
Alanine aminotransferase (ALT)	$\leq 3 \times$ ULN

[2] Cockcroft-Gault formula will be used to calculate creatinine clearance (See SPM)

11. Women of childbearing potential must have a negative serum or urine pregnancy.

12. Women of childbearing potential (WOCBP) and male subjects must use appropriate method(s) of contraception as outlined in Section 5.6

3.2 Exclusion Criteria

Subjects meeting any of the criteria below may not participate in the study:

1. Active infection requiring systemic therapy.

2. Pregnant or breastfeeding (**NOTE:** breast milk cannot be stored for future use while the mother is being treated on study).

3. Any serious or uncontrolled medical disorder that, in the opinion of the site investigator, may increase the risk associated with study participation or study drug administration, impair the ability of the subject to receive protocol therapy, or interfere with the interpretation of study results.

4. Prior malignancy active within the previous 3 years except for locally curable cancers that have been apparently cured.

5. Subjects with active, known or suspected autoimmune disease. Subjects with vitiligo, type I diabetes mellitus, residual hypothyroidism due to autoimmune condition only requiring hormone replacement, psoriasis not requiring systemic treatment, or conditions not expected to recur in the absence of an external trigger are permitted to enroll.

6. Subjects with a condition requiring systemic treatment with either corticosteroids (> 10 mg daily prednisone equivalents) or other immunosuppressive medications within 14 days of

study drug administration. Inhaled or topical steroids and adrenal replacement doses > 10 mg daily prednisone equivalents are permitted in the absence of active autoimmune disease.

7. Prior treatment with an anti-PD-1, anti-PD-L1, anti-PD-L2, anti-CTLA-4 antibody, or any other antibody or drug specifically targeting T-cell co-stimulation or immune checkpoint pathways.

8. Grade ≥ 2 neuropathy (NCI CTCAE version 4).

9. Known positive result for hepatitis B virus surface antigen (HBV sAg) or hepatitis C virus ribonucleic acid (RNA) or hepatitis C antibody (HCV antibody) indicating acute or chronic infection. Testing at screening is not required.

10. Known history of testing positive for human immunodeficiency virus (HIV) or known acquired immunodeficiency syndrome (AIDS).

11. Evidence of interstitial lung disease or active, non-infectious pneumonitis.

12. Significant cardiovascular disease, such as New York Heart Association cardiac disease (Class III or greater), myocardial infarction within 3 months prior to randomization, unstable arrhythmias, or unstable angina.

13. Known left ventricular ejection fraction (LVEF) < 40% Patients with known coronary artery disease, congestive heart failure not meeting the above criteria, or LVEF 40%−50% must be on a stable medical regimen that is optimized in the opinion of the treating physician, in consultation with a cardiologist if appropriate.

14. Solid organ or tissue transplant including stem cell transplant.

4. SUBJECT REGISTRATION

All subjects must be registered through HCRN's electronic data capture (EDC) system. A subject is considered registered when an "on study" date is entered into the EDC system.

Subjects must be registered and randomized prior to starting protocol therapy. Subjects must begin therapy **within 7 business days** of registration.

4.1 Randomization and Stratification

Randomization will be stratified on the metastasis status (unresectable primary and/or lymph node only vs. the rest).

5. TREATMENT PLAN

Patients will be randomized to Arm A: gemcitabine plus carboplatin plus nivolumab versus Arm B: gemcitabine plus oxaliplatin plus nivolumab. Randomization will be stratified on the metastasis status (lymph node only vs. the rest). Patients on both treatment arms will receive up to 6 cycles of combination therapy in the absence of prohibitive adverse effects or disease progression. Patients with at least stable disease at the completion of 6 cycles of treatment may continue "maintenance" single agent nivolumab for up to 12 cycles. Patients who require discontinuation of chemotherapy (i.e., gemcitabine plus carboplatin or gemcitabine plus oxaliplatin) prior to Cycle 6, but who have at least stable disease, may be considered for ongoing treatment with single-agent nivolumab on the "maintenance" phase after discussion with the sponsor-investigator.

5.1 Pre-Medication Guidelines

5.1.1 Gemcitabine, Carboplatin or Oxaliplatin

Institutional standards may be used for infusion of chemotherapy including premedication administration. **NOTE:** Infusions may be given ± 2 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. Body surface area and chemotherapy drug dose recalculations may occur per institutional standards.

5.1.2 Nivolumab

There are no required premedications for the administration of nivolumab. **NOTE:** Infusions may be given ± 2 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. An infusion window of ± 10 minutes may be applied.

5.2 Medication Administration

For both Arms A and B, the sequence of administration should be nivolumab → gemcitabine → platinum agent. *Nivolumab will be administered prior to any other chemotherapy with at least a **30-minute period** between nivolumab administration and the initial chemotherapy.*

Arm A: Nivolumab, Gemcitabine, and Carboplatin

Agent	Route	Dose	Administration Time		Frequency (± 3 days)	Cycle Length	Total # Cycles
Nivolumab	IV	360 mg	30 minutes (± 10 minutes)		Day 1	21 days	6
Gemcitabine	IV	1000 mg/m^2	Per institutional guidelines		Day 1, 8		
Carboplatin	IV	AUC 4.5[1]	Per institutional guidelines		Day 1		

[1]Carboplatin dosing will be based on the Calvert formula [dose (mg) = AUC (mg ml-1 min) x [GFR (ml/min) + 25 (ml/min)] Creatinine clearance calculated according to the Cockroft Gault equation to estimate the GFR.

Arm B: Nivolumab, Gemcitabine, and Oxaliplatin

Agent	Route	Dose	Administration Time	Frequency (± 3 days)	Cycle Length	Total # Cycles
Nivolumab	IV	360 mg	30 minutes (± 10 minutes)	Day 1	21 days	6
Gemcitabine	IV	1000 mg/m^2	Per institutional guidelines	Day 1, 8		
Oxaliplatin	IV	130 mg/m^2	Per institutional guidelines	Day 1		

Maintenance Single Agent Nivolumab (starting ~ 2-4 weeks after completing combination chemotherapy plus nivolumab)

Agent	Route	Dose	Administration Time	Frequency (± 3 days)	Cycle Length	Total # Cycles
Nivolumab	IV	480 mg	30 minutes (± 10 minutes)	Day 1	28 days	12

5.3 Concomitant Medications

5.3.1 Allowed Concomitant Medications

Medications or vaccinations specifically prohibited in the exclusion criteria are not allowed during the ongoing trial. If there is a clinical indication for any medication or vaccination specifically prohibited during the trial, discontinuation from trial therapy or vaccination may be required. The site investigator should discuss any questions regarding this with the sponsor-investigator. The final decision on any supportive therapy or vaccination rests with the site investigator and/or the subject's primary physician. However, the decision to continue the subject on trial therapy or vaccination schedule requires the mutual agreement of the site investigator, the sponsor-investigator and the subject.

- All treatments that the site investigator considers necessary for a subject's welfare may be administered at the discretion of the treating investigator in keeping with the community standards of medical care.
- All concomitant medications received within 30 days before the first dose of trial treatment and 30 days after the last dose of trial treatment should be recorded.
- Concomitant therapy includes any prescription medications or over-the-counter preparations used by a patient between the 7 days preceding the screening evaluation and the treatment discontinuation visit.

5.3.2 Prohibited Concomitant Medications

Subjects are prohibited from receiving the following therapies during the Treatment Phase of this trial:

- Antineoplastic systemic chemotherapy or biological therapy not specified in this protocol
- Immunotherapy not specified in this protocol

5.4 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 ASCO guidelines. Growth factors should be not used during Cycle #1 or in lieu of recommended dose reductions.

Radiation therapy to a solitary symptomatic site may be considered on a case by case basis after discussion with the sponsor-investigator.

5.6 Reproductive Information

5.6.1 Women Subjects of Childbearing Potential

Women subjects of childbearing potential who are sexually active and their partners must agree to abstain from heterosexual intercourse or to use 2 forms of effective methods of contraception beginning with time of consent, during the study treatment and for 5 months days after last dose of nivolumab (or timeframe outlined per package insert for chemotherapy). This timeframe also applies to breast feeding. Two contraception methods can be comprised of two barrier methods, or a barrier method plus a hormonal method.

NOTE: Women of childbearing potential is defined as any female who has experienced menarche and who has not undergone surgical sterilization (hysterectomy or bilateral oophorectomy) or who is not postmenopausal. Menopause is defined clinically as 12 months of amenorrhea in a woman over 45 in the absence of other biological or physiological causes. In addition, women under the age of 62 must have a documented serum follicle stimulating hormone (FSH) level less than 40 mIU/mL.

5.6.2 Male Subjects Capable of Fathering a Child

Male subjects capable of fathering a child that are sexually active with partners of childbearing potential must agree to abstain from heterosexual intercourse or to use 2 forms of effective methods of contraception beginning with time of consent, during the study treatment and for the timeframe outlined per package insert for chemotherapy. This timeframe also applies to sperm donation. Two contraception methods can be comprised of two barrier methods, or a barrier method plus a hormonal method.

5.6.3 Methods of Contraception

HIGHLY EFFECTIVE METHODS OF CONTRACEPTION

- Male condoms with spermicide
- Hormonal methods of contraception including combined oral contraceptive pills, vaginal ring, injectables, implants and intrauterine devices (IUDs) such as Mirena® by WOCBP subject.
- Nonhormonal IUDs, such as ParaGard®
- Tubal ligation
- Vasectomy
- Complete Abstinence*

*Complete abstinence is defined as complete avoidance of heterosexual intercourse and is an acceptable form of contraception for all study drugs. Subjects who choose complete abstinence are not required to use a second method of contraception, but female subjects must continue to have pregnancy tests. Acceptable alternate methods of highly effective contraception must be discussed in the event that the subject chooses to forego complete abstinence.

LESS EFFECTIVE METHODS OF CONTRACEPTION

- Diaphragm with spermicide
- Cervical cap with spermicide
- Vaginal sponge
- Male condom without spermicide
- Progestin only pills by WOCBP subject or male subject's WOCBP partner
- Female condom (A male and female condom must not be used together)

6. DOSE DELAYS/MODIFICATIONS

The NCI Common Terminology Criteria for Adverse Events (CTCAE) v4 will be used to grade adverse events. Subjects 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. Subjects 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.

6.1 Initiation of New Cycle of Treatment

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 (provided criteria in Section 6.7 also met):

- ANC $\geq$ 1.5 K/mm^3
- Platelets $\geq$ 100 K/mm^3
- Resolution of non-hematologic toxicities to $\leq$ Grade 1 or baseline
- AST, ALT and $\leq$ 3.0 x ULN

Subjects requiring treatment to be held for toxicity > 4 weeks will be removed from study treatment and should proceed with definitive management of their tumor as per their treatment physician.

6.2 Treatment Limiting Adverse Event

A treatment-limiting adverse event is any adverse event related to study treatment (includes carboplatin or oxaliplatin, gemcitabine and nivolumab) experienced during the study resulting in treatment termination.

6.3 Dose Adjustments for Gemcitabine, Carboplatin, and Oxaliplatin

The following dose reductions should be utilized as directed by the guidance detailed in Sections 6.4-6.6.

Dose level	**Gemcitabine**	**Carboplatin**	**Oxaliplatin**
Dose level -1	800 mg/m^2	AUC 4	100 mg/m^2
Dose level -2	600 mg/m^2	AUC 3.5	80 mg/m^2

6.4 Dose Delays/Modifications for Treatment Related Hematological Toxicity

Treatment with nivolumab will also be HELD until patients meet criteria to resume dosing with gemcitabine and carboplatin or gemcitabine and oxaliplatin respectively.

Gemcitabine and Carboplatin/Oxaliplatin Dose Reductions for Hematologic Toxicity

Neutrophils (x10^9 cells/L)		Platelets (x 10^9 cells/L)	Gemcitabine Dose	Carboplatin Dose	Oxaliplatin Dose
Day 1					
≥1.5	AND	≥100	100%	AUC 4.5	-
≥1.5	AND	≥100	100%	-	130 mg/m2
<1.5	OR	<100	Delay*	Delay*	-
<1.5	OR	<100	Delay*	-	Delay*
Day 8					
≥1.5	AND	≥100	100%	-	-
1.0-<1.5	AND	≥100	Reduce 1 dose level	-	-
<1.0	OR	<100	Delay**	-	-

*Once ANC ≥ 1500 and platelets ≥ 100,000, resume therapy with gemcitabine reduced by 1 dose level. If gemcitabine has already been reduced to dose level -1, reduce carboplatin/oxaliplatin by 1 dose level. If gemcitabine and carboplatin/oxaliplatin have already been reduced to dose level -1, reduce gemcitabine to dose level -2. If gemcitabine has already been reduced to dose level -2, discuss dose reduction with sponsor-investigator. Granulocyte colony stimulating factors may be used at the discretion of the site investigator; however, growth factors should be not used during cycle #1 or in lieu of recommended dose reductions.

**If ANC ≥ 1500 and platelets ≥ 100,000 within 14 days, proceed with "Day 8" gemcitabine reduced by 1 dose level. If gemcitabine has already been reduced to dose level -2, discuss further dose reductions with sponsor-investigator. If dose delay >14 days required for recovery of ANC ≥ 1500 and platelets ≥ 100,000, omit "Day 8" dose of cycle and resume treatment with the subsequent cycle of treatment with gemcitabine and carboplatin/oxaliplatin reduced by 1 dose level. If gemcitabine has already been reduced to dose level -2, discuss dose reduction with sponsor-investigator.

If gemcitabine plus carboplatin/oxaliplatin is held on Day 1 of a treatment cycle for hematologic toxicity as outlined above, nivolumab will also be held until criteria are met to initiate the cycle of treatment.

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

6.5 Febrile Neutropenia

If febrile neutropenia develops in a given cycle, hold gemcitabine, carboplatin/oxaliplatin, and nivolumab during febrile neutropenia.

Resume gemcitabine and carboplatin/oxaliplatin at one dose lower than the dose administered in the last cycle. This dose should be used for all subsequent cycles. The dose of nivolumab will be unchanged. Granulocyte colony stimulating factors may be used at the discretion of the site investigator.

6.6 Dose Delays/Modifications for Other Treatment Related Non-Hematological Toxicity Secondary to Gemcitabine or Carboplatin/Oxaliplatin

Dose delays/reductions for non-hematologic toxicities attributable to gemcitabine or carboplatin/oxaliplatin (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 site investigator should be dose reduced. Patients with treatment-related nausea that is Grade ≥ 2 despite optimal use of antiemetics will be dose reduced by 1 dose level. If the Day 8 dose of gemcitabine is held for non-hematologic toxicity, the "Day 8" dose of gemcitabine may be administered the following week provided the adverse event was adequately improved or resolved. If the adverse event has not adequately improved or resolved within 2 weeks, the "Day 8" dose of gemcitabine should be held for that cycle and treatment should resume (once the adverse event improves/resolves) with the next cycle of treatment.

Dose Reductions of Gemcitabine/Carboplatin/Oxaliplatin for Non-Hematologic Toxicities*

Non-Hematologic toxicity	Gemcitabine/Carboplatin/Oxaliplatin
Grade 0-2	No change
Grade 3	Hold until Grade ≤ 1 and resume treatment reduced by 1 dose level
Grade 4	Hold until Grade ≤ 1 and resume treatment reduced by 1 dose level

*See specific guidance for oxaliplatin-related neuropathy below

Dose Reductions for Oxaliplatin-related Neuropathy

Neuropathy grade	Oxaliplatin dose
Grade 1	No change
Grade 2 (persisting until next cycle)	100 mg/m2
Grade 3 (>7 days but resolved before next cycle)	100 mg/m2
Grade 3 (persisting until next cycle) or 4	Discontinue

Dose re-escalation after a dose reduction for non-hematologic toxicity should not occur without discussion with the sponsor-investigator.

If toxicity is specifically attributable to gemcitabine or carboplatin/oxaliplatin and warrants discontinuation of that particular agent, patients may be considered for continuation on treatment with carboplatin/oxaliplatin (or gemcitabine) and nivolumab but this must be discussed with the sponsor-investigator.

6.7 Dose Modifications for Nivolumab

Dose reductions or dose escalations are not permitted.

6.7.1 Dose Delay Criteria

Because of the potential for clinically significant nivolumab-related AEs requiring early recognition and prompt intervention, management algorithms have been developed for suspected AEs of selected categories. [see current Investigator Brochure and Appendix A]
Dose delay criteria apply for all drug-related adverse events (regardless of whether or not the event is attributed to nivolumab). All study drugs must be delayed until treatment can resume. In rare circumstances, treatment with gemcitabine plus carboplatin/oxaliplatin could potentially be continued in the setting of select adverse events related to nivolumab after discussion and approval from the sponsor-investigator.

Nivolumab administration should be delayed for the following:
Any Grade ≥ 2 non-skin, drug-related AE, with the following exceptions:

- Grade 2 drug-related fatigue or laboratory abnormalities do not require a treatment delay
- Any Grade 3 skin, drug-related AE
- Any Grade 3 drug-related laboratory abnormality, with the following exceptions for lymphopenia, leukopenia, AST, ALT, total bilirubin, or asymptomatic amylase or lipase:
- Grade 3 lymphopenia or leukopenia does not require dose delay.
- If a subject has a baseline AST, ALT, or total bilirubin that is within normal limits, delay dosing for drug-related Grade ≥ 2 toxicity.
- If a subject has baseline AST, ALT, or total bilirubin within the Grade 1 toxicity range, delay dosing for drug-related Grade ≥ 3 toxicity.
- Any Grade ≥ 3 drug-related amylase or lipase abnormality that is not associated with symptoms or clinical manifestations of pancreatitis does not require dose delay. The sponsor-investigator should be consulted for such Grade ≥ 3 amylase or lipase abnormalities.

Any AE, laboratory abnormality, or intercurrent illness which, in the judgment of the site investigator, warrants delaying the dose of study medication.

Subjects who require delay of nivolumab should be re-evaluated weekly or more frequently if clinically indicated and resume nivolumab dosing when re-treatment criteria are met.

6.7.2 Criteria to Resume Treatment

Subjects may resume treatment with nivolumab when the drug-related AE(s) resolve to Grade ≤1 or baseline value, with the following exceptions:

- Subjects may resume treatment in the presence of Grade 2 fatigue
- Subjects who have not experienced a Grade 3 drug-related skin AE may resume treatment in the presence of Grade 2 skin toxicity
- Subjects with baseline Grade 1 AST/ALT or total bilirubin who require dose delays for reasons other than a 2-grade shift in AST/ALT or total bilirubin may resume treatment in the presence of Grade 2 AST/ALT OR total bilirubin
- Subjects with combined Grade 2 AST/ALT AND total bilirubin values meeting discontinuation parameters should have treatment permanently discontinued
- Drug-related pulmonary toxicity, diarrhea, or colitis, must have resolved to baseline before treatment is resumed.
- Drug-related endocrinopathies adequately controlled with only physiologic hormone replacement may resume treatment.

If the criteria to resume treatment are met, the subject should restart treatment at the next scheduled timepoint per protocol. However, if the treatment is delayed past the next scheduled timepoint per protocol, the next scheduled timepoint will be delayed until dosing resumes.

If treatment is delayed or interrupted for > 4 weeks, the subject must be permanently discontinued from study therapy, and should proceed with definitive treatment of their primary tumor as per their treating physician, unless otherwise discussed and approved by sponsor-investigator (e.g., in the setting of completion of a steroid taper).

6.7.3 Management Algorithms for Immune-Related Events

Guidelines for the management of immune related events can be found in the current Investigator Brochure AND in the Appendix A. Site investigators should decide the appropriate source of AE management for each protocol.

Immuno-oncology (I-O) agents are associated with AEs that can differ in severity and duration than AEs caused by other therapeutic classes. Nivolumab is considered an immuno-oncology agent in this protocol. Early recognition and management of AEs associated with immuno-oncology agents may mitigate severe toxicity. Management algorithms have been developed to assist investigators in assessing and managing the following groups of AEs: Gastrointestinal, Renal, Pulmonary, Hepatic, Endocrinopathies, Skin, Neurological.

For subjects expected to require more than 4 weeks of corticosteroids or other immunosuppressants to manage an AE, consider recommendations provided in the algorithms. These algorithms are found in the Nivolumab IB [and in Appendix A] of this protocol. The

guidance provided in these algorithms should not replace the site investigator's medical judgment but should complement it.

6.7.4 Treatment of Nivolumab Related Infusion Reactions

Since nivolumab contains only human immunoglobulin protein sequences, it is unlikely to be immunogenic and induce infusion or hypersensitivity reactions. However, if such a reaction were to occur, it might manifest with fever, chills, rigors, headache, rash, pruritis, arthralgias, hypo- or hypertension, bronchospasm, or other symptoms of allergic-like reactions.

All Grade 3 or 4 infusion reactions should be reported as an SAE if criteria are met. Infusion reactions should be graded according to NCI CTCAE v4 guidelines.

Treatment recommendations are provided below and may be modified based on local treatment standards and guidelines as appropriate:

For Grade 1 symptoms: (Mild reaction; infusion interruption not indicated; intervention not indicated)

- Remain at bedside and monitor subject until recovery from symptoms. The following prophylactic premedications are recommended for future infusions: diphenhydramine 50 mg (or equivalent) and/or paracetamol 325 to 1000 mg (acetaminophen) at least 30 minutes before additional nivolumab administrations.

For Grade 2 symptoms: (Moderate reaction requires therapy or infusion interruption but responds promptly to symptomatic treatment [e.g., antihistamines, non-steroidal anti-inflammatory drugs, narcotics, corticosteroids, bronchodilators, IV fluids]; prophylactic medications indicated for 24 hours).

- Stop the nivolumab infusion, begin an IV infusion of normal saline, and treat the subject with diphenhydramine 50 mg IV (or equivalent) and/or paracetamol 325 to 1000 mg (acetaminophen); remain at bedside and monitor subject until resolution of symptoms. Corticosteroid or bronchodilator therapy may also be administered as appropriate. If the infusion is interrupted, then restart the infusion at 50% of the original infusion rate when symptoms resolve; if no further complications ensue after 30 minutes, the rate may be increased to 100% of the original infusion rate. Monitor subject closely. If symptoms recur then no further nivolumab will be administered at that visit. Administer diphenhydramine 50 mg IV, and remain at bedside and monitor the subject until resolution of symptoms. The amount of study drug infused must be recorded on the electronic case report form (eCRF). The following prophylactic premedications are recommended for future infusions: diphenhydramine 50 mg (or equivalent) and/or paracetamol 325 to 1000 mg (acetaminophen) should be administered at least 30 minutes before additional nivolumab administrations. If necessary, corticosteroids (recommended dose: up to 25 mg of IV hydrocortisone or equivalent) may be used.

For Grade 3 or Grade 4 symptoms: (Severe reaction, Grade 3: prolonged [i.e., not rapidly responsive to symptomatic medication and/or brief interruption of infusion]; recurrence of symptoms following initial improvement; hospitalization indicated for other clinical sequelae [e.g., renal impairment, pulmonary infiltrates]). Grade 4: (life threatening; pressor or ventilatory support indicated).

- Immediately discontinue infusion of nivolumab. Begin an IV infusion of normal saline, and treat the subject as follows. Recommend bronchodilators, epinephrine 0.2 to 1 mg of a 1:1,000 solution for subcutaneous administration or 0.1 to 0.25 mg of a 1:10,000 solution injected slowly for IV administration, and/or diphenhydramine 50 mg IV with methylprednisolone 100 mg IV (or equivalent), as needed. Subject should be monitored until the investigator is comfortable that the symptoms will not recur. Nivolumab will be permanently discontinued. Investigators should follow their institutional guidelines for the treatment of anaphylaxis. Remain at bedside and monitor subject until recovery from symptoms.

In the case of late-occurring hypersensitivity symptoms (e.g., appearance of a localized or generalized pruritis within 1 week after treatment), symptomatic treatment may be given (e.g., oral antihistamine, or corticosteroids).

6.8 Discontinuation Criteria for Nivolumab

Treatment with nivolumab should be permanently discontinued for the following (while all study therapy should be discontinued for the majority of these scenarios, there are rare situations in which it could be acceptable to continue treatment with gemcitabine plus carboplatin/oxaliplatin despite discontinuing nivolumab. Continuing treatment with gemcitabine plus carboplatin/oxaliplatin should be discussed and approved by the sponsor-investigator):

- Any Grade 2 drug-related uveitis or eye pain or blurred vision that does not respond to topical therapy and does not improve to Grade 1 severity within the re-treatment period OR requires systemic treatment
- Any Grade 3 non-skin, drug-related adverse event lasting > 7 days, with the following exceptions for drug-related laboratory abnormalities, uveitis, pneumonitis, bronchospasm, hypersensitivity reactions, and infusion reactions, and endocrinopathies:
    - Grade 3 drug-related uveitis, pneumonitis, bronchospasm, hypersensitivity reaction, or infusion reaction of any duration requires discontinuation
    - Grade 3 drug-related endocrinopathies adequately controlled with only physiologic hormone replacement do not require discontinuation
    - Grade 3 drug-related laboratory abnormalities do not require treatment discontinuation except those noted below
- Grade 3 drug-related thrombocytopenia > 7 days or associated with bleeding requires discontinuation
- Any drug-related liver function test (LFT) abnormality that meets the following criteria require discontinuation:
    - AST or ALT > 5 x ULN
    - Total bilirubin > 3 x ULN
    - Concurrent AST or ALT > 3 x ULN and total bilirubin > 2 x ULN

- Any Grade 4 drug-related adverse event or laboratory abnormality, except for the following events which do not require discontinuation:
    - Isolated Grade 4 amylase or lipase abnormalities that are not associated with symptoms or clinical manifestations of pancreatitis and decrease to < Grade 4 within 1 week of onset.
    - Isolated Grade 4 electrolyte imbalances/abnormalities that are not associated with clinical sequelae and are corrected with supplementation/appropriate management within 72 hours of their onset
    - Grade 4 lymphopenia or leukopenia
    - Grade 4 drug-related endocrinopathy adverse events, such as adrenal insufficiency, ACTH deficiency, hyper- or hypothyroidism, or glucose intolerance, which resolve or are adequately controlled with physiologic hormone replacement (corticosteroids, thyroid hormones) or glucose-controlling agents, respectively, may not require discontinuation after discussion with and approval from the sponsor-investigator [as allowed by protocol]
- Any dosing interruption lasting > 6 weeks with the following exceptions (these potential exceptions must be reviewed and approved by the sponsor-investigator):
    - Dosing delays or interruptions to allow for prolonged steroid tapers to manage drug-related adverse events are allowed. Prior to re-initiating treatment in a subject with a dosing interruption lasting > 6 weeks, the Investigator must be consulted. Tumor assessments should continue as per protocol even if dosing is interrupted or delayed
    - Dosing interruptions or delays lasting > 6 weeks that occur for non-drug-related reasons may be allowed if approved by the sponsor-investigator. Prior to re-initiating treatment in a subject with a dosing interruption lasting > 6 weeks, the sponsor-investigator must be consulted. Tumor assessments should continue as per protocol even if dosing is interrupted
- Any adverse event, laboratory abnormality, or intercurrent illness which, in the judgment of the site investigator, presents a substantial clinical risk to the subject with continued nivolumab dosing

6.9 Protocol Therapy Discontinuation

In addition to discontinuation from therapy related to toxicities, a subject will also be discontinued from protocol therapy and followed per protocol under the following circumstances outlined below. The reason for discontinuation of protocol therapy will be documented on the electronic case report form (eCRF)

- Documented disease progression
- Site investigator determines a change of therapy would be in the best interest of the subject
- Subject requests to discontinue protocol therapy, whether due to unacceptable toxicity or for other reasons. **NOTE:** If a subject decides to prematurely discontinue protocol therapy ("refuses treatment"), the subject should be asked if he or she may still be contacted for further scheduled study assessments. The outcome of that discussion should be documented in both the medical records and in the eCRF.
- Female subject becomes pregnant
- Protocol therapy interruptions as defined above

6.10 Protocol Discontinuation

If a subject decides to discontinue from the protocol (and not just from protocol therapy) all efforts should be made to complete and report study assessments as thoroughly as possible. A complete final evaluation at the time of the subject's protocol withdrawal should be made with an explanation of why the subject is withdrawing from the protocol. If the reason for removal of a subject from the study is an adverse event, it will be recorded on the eCRF.

7. STUDY CALENDAR & EVALUATIONS

Study Evaluation Cycle = 21 days	Screening	Treatment Cycles 1-6		Disease Progression[12]	Safety follow up visit[13]	Long-term Follow up[14]
	-28 days	Day 1 ± 2 days	Day 8 ± 2 days		30/100 days post last dose	± 14 days
REQUIRED ASSESSMENTS						
Informed Consent	X					
Medical History including Smoking History[1]	X					
Physical Exam	X	X			D30	
Vital signs and ECOG Performance Status[2]	X	X			D30	
AEs & concomitant medications	X	X	X		X	
LABORATORY ASSESSMENTS						
Complete Blood Cell Count with diff (CBC)	X	X[4]	X		D30	
Comprehensive Metabolic Profile (CMP)[3]	X	X[4]	X		D30	
Amylase and Lipase		X				
PT/INR and aPTT	X					
Thyroid Function (TSH, T4, free T3)[5]	X	X[5]				
Pregnancy test (serum or urine) (WOCBP)[6]	X					
DISEASE ASSESSMENT						
CT of chest[7]	X	After Cycle 3 and Cycle 6		X		X[14]
CT or MRI of abdomen and pelvis[7]	X			X		X[14]
TREATMENT						
Arm A: Gemcitabine + Carboplatin		X				
Arm B: Gemcitabine + Oxaliplatin		X				
Gemcitabine			X			
Nivolumab		X				
SPECIMEN COLLECTION						
Archival Tumor Tissue[8]	X					
Tumor tissue (obtained for standard clinical purposes)[9]				X		
Blood for germline[10]		C1D1				
Whole Blood[11]		X[11]				
PBMCs[11]		X[11]		X[11]	D30[11]	
Plasma[11]		X[11]		X[11]	D30[11]	
FOLLOW-UP						
Survival Status, Subsequent Therapy						X

Key to Footnotes

[1.] Medical History to include smoking questionnaire and a question about how the subject became aware of this clinical trial. Should also include diagnosis and staging information: Tumor Node Metastasis (TNM). Prior genomic or molecular results, performed in laboratories for standard clinical purposes (e.g., targeted DNA sequencing panels for "actionable" mutations) are required if available.

[2] Vital signs to include blood pressure, weight, and ECOG performance status. Height should be obtained at screening only.

[3] CMP to include sodium, potassium, chloride, creatinine, blood urea nitrogen; liver function tests (LFTs) to include AST, ALT, total bilirubin, alkaline phosphatase

[4] If screening (baseline) CBC and CMP were performed within 7 days of Day 1 of treatment, these do not need to be repeated.

[5] Thyroid function testing will be done every other cycle during treatment. TSH, T3 and T4 should be performed; free versus total for T3 and T4 is at the site investigator's discretion.

[6] For women of childbearing potential (WOCBP): urine or serum βhCG, within 7 days prior to Day 1.

[7] Tumor response assessment will be performed by the site investigator and will consist of evaluation by CT scans of chest and MRI or CT of abdomen and pelvis. Imaging selected for each subject should remain the same throughout the study if at all possible. An MRI is strongly suggested if the subject cannot have contrast for the CT scans. Tumor imaging to be done at treatment discontinuation at discretion of site investigator. If tumor assessments are available for subjects who have not yet experienced progressive disease (PD) at the time treatment is discontinued, the follow-up tumor evaluations will be documented in the eCRF until PD or death is confirmed, or until another treatment is initiated. A bone scan will be obtained at baseline if any clinical or laboratory suspicion of metastatic bone involvement. If a bone scan is positive at baseline for metastases, it will be included with tumor response assessments as noted above.

[8] Archival tissue: Representative formalin-fixed paraffin-embedded (FFPE) tumor specimens (metastatic specimens preferable but if not available primary tumor specimens that are at least muscle-invasive are acceptable) in paraffin blocks (blocks preferred) or at least 15 unstained slides. If archival tissue is not available, subjects may be considered for enrollment on a case by case basis after discussion with the sponsor-investigator. Stored samples will be reserved for future unspecified cancer-related research. See Correlative Laboratory Manual (CLM) for additional details.

[9] Surplus tissue remaining after routine standard of care procedures (e.g., biopsy of a metastatic lesion) will be collected during this study and stored for future unspecified cancer-related research.

[10] Peripheral blood will be collected for somatic baseline prior to treatment on C1D1.

[11] Serial blood samples will be collected to support biomarker research. These samples will be separated into whole blood, plasma and PBMCs. Timepoints for collection of whole blood: C1D1, C2D1, C3D1; timepoints for PBMCs C1D1, C3D1, progression/safety visit; timepoints for plasma C1D1, C2D1, C3D1, progression/safety visit. See CLM and Table 4 for additional details.

[12] Subjects with suspected clinical progression should undergo imaging (CT chest and CT or MRI abdomen and pelvis) to document disease progression. An MRI is strongly suggested if the subject cannot have contrast for the CT scans. Bone scans should also be performed in the setting of suspicion of bone metastases. Blood samples for research purposes should be collected at the time of disease progression (Table 4).

[13]The initial safety follow-up visit should only occur when subjects permanently stop study treatment for whatever reasons (toxicity, progression, or at discretion of site investigator) and should be performed 30 days (±7 days) after the last dose of treatment. Subjects who have an ongoing ≥ grade 2 or serious AE (SAE) at this visit will continue to be followed until the AE resolves to ≤ Grade 1 or baseline, deemed clinically insignificant, and/or until a new anti-cancer treatment starts, whichever is earlier. Subjects discontinuing study treatment for disease progression who have not already had blood samples drawn for research purposes (Table 4) at "progression" should have specimens drawn at this visit. The D100 (± 7 days) safety visit will consist of a phone call, email or other avenues as appropriate to assess AEs.

[14] Subjects who discontinue treatment for any reason without documented disease progression will be followed for disease progression every 3 months x 1.5 years, every 6 months x 1.5 years, and then yearly x 2 years (from treatment discontinuation). Once disease progression is documented, subjects will enter a survival follow up period every 6 months for 2 years from the time of documented progression. Follow up may be accomplished via clinic visit, phone call, or other avenues as appropriate. Subjects who complete 6 cycles of combination therapy and have no evidence of disease progression or prohibitive adverse events should proceed with "maintenance" single agent nivolumab as detailed in the calendar of events below. Subjects who require discontinuation of chemotherapy (i.e., gemcitabine plus carboplatin or gemcitabine plus oxaliplatin) prior to cycle 6, but who have at least stable disease, may be considered for ongoing treatment with single-agent nivolumab on the "maintenance" phase after discussion with the sponsor-investigator. Long term follow up visits have a window ± 14 days.

Maintenance Phase (only patients who have at least stable disease after completion of 6 cycles of chemotherapy plus nivolumab and for select patients who have at least stable disease but require discontinuation of chemotherapy prior to cycle 6 due to adverse events).

Maintenance treatment should be initiated ~ 2-4 weeks after completing combination chemotherapy plus nivolumab).

Study Evaluation Cycle = 28 days Maintenance Phase = Cycles 7-18	Maintenance Cycles 7-18	Disease progression	Safety follow up visit[8]	Long-term Follow up[9]
	Day 1 ± 2 days		30/100 days post last dose ± 7 days	± 14 days
REQUIRED ASSESSMENTS				
Physical Exam	X		D30	
Vital signs and ECOG Performance Status[1]	X		D30	
AEs & concomitant medications	X		X	
LABORATORY ASSESSMENTS				
Complete Blood Cell Count with diff (CBC)	X		D30	
Comprehensive Metabolic Profile (CMP)[2]	X		D30	
Thyroid Function (TSH, T4, free T3)[3]	X			
Amylase and Lipase[3]	X			
DISEASE ASSESSMENT				
CT of chest[4]	X[4]	X[7]		X
CT or MRI of abdomen and pelvis[4]	X[4]	X[7]		X
TREATMENT				
Nivolumab	X			
SPECIMEN COLLECTION				
Tumor tissue (obtained for standard clinical purposes)[5]		X[5]		X
PBMCs[6]	X[6]	X[6]	D30[6]	
Plasma[6]	X[6]	X[6]	D30[6]	
FOLLOW-UP				
Survival Status, Subsequent Therapy				X

Key to Footnotes

1: Vital signs to include blood pressure, weight, and ECOG performance status.

2: CMP to include sodium, potassium, chloride, creatinine, blood urea nitrogen; liver function tests (LFTs) to include AST, ALT, total bilirubin, alkaline phosphatase

3: Thyroid function, amylase, and lipase testing will be done every other cycle during treatment. TSH, T3 and T4 should be performed; free versus total for T3 and T4 is at the site investigator's discretion.

4: Tumor response assessment will be performed by the site investigator and will consist of evaluation by CT scan of the chest and MRI or CT scan of abdomen and pelvis (imaging selected for each subject should remain the same throughout the study if at all possible). An MRI is strongly suggested if the subject cannot have contrast for the CT scans. If tumor assessments are available for subjects who have not yet experienced progressive disease (PD) at the time treatment is discontinued, the follow-up tumor evaluations will be documented in the eCRF until PD or death is confirmed, or until another treatment is initiated. A bone scan will be obtained if any clinical or laboratory suspicion of metastatic bone involvement. If a bone scan is positive at baseline for metastases, it will be included with tumor response assessments as noted above. Tumor response assessment should occur every 3 months.

5: Surplus fixed paraffin-embedded blocks/slides tissue remaining after routine standard of care procedures (e.g., biopsy of a metastatic lesion) will be collected during this study and stored for future cancer-related research. See CLM for additional details.

6: Blood samples will be collected to support biomarker research. Time points for collection of whole blood, PBMCs and plasma include C8D1 and PBMCs and plasma at time of progression or Safety follow up visit. See Table 4 and CLM for additional details.

7: Subjects with suspected clinical evidence of disease progression should undergo cross sectional imaging (i.e., CT chest and CT or MRI abdomen and pelvis). An MRI is strongly suggested if the subject cannot have contrast for the CT scans. Bone scans should also be performed in the setting of suspicion of bone metastases. Blood samples for research purposes should be collected at the time of disease progression (Table 4).

8: Safety follow-up visit should 30 days (±7 days) after the last dose of treatment when subjects permanently stop study treatment for whatever reasons (toxicity, progression, or at discretion of site investigator). Subjects who have an ongoing ≥ grade 2 or serious AE (SAE) at this visit will continue to be followed until the AE resolves to ≤ Grade 1 or baseline, deemed clinically insignificant, and/or until a new anti-cancer treatment starts, whichever is earlier. Blood samples to support biomarker research will be collected at the time of safety follow-up visit unless already drawn within the prior 30 days. The D100 (± 7 days) safety visit will consist of a phone call, email or other avenues as appropriate to assess AEs.

9: Subjects who discontinue treatment for any reason without documented disease progression will be followed for disease progression every 3 months x 1.5 years, every 6 months x 1.5 years, and then yearly x 2 years from initiation of study treatment. Once disease progression is documented, subjects will enter a survival follow up period every 6 months for 2 years from the time of documented progression. Follow up may be accomplished via clinic visit, phone call, or other avenues as appropriate. Long term follow up visits have a window ± 14 days..

Table 4. Schedule for correlative blood sample collections

Visit	Sample	Purpose	Collection
Screening	Archival Tissue	Outlined correlative studies and banking	Block and H&E or 15 unstained slides and H&E
Follow Up	Standard of Care Biopsies	Outlined correlative studies and of post treatment tumor tissue	Block and H&E or 15 unstained slides and H&E
C1D1	PBMCs	T-cells	3 x 8.5 ml ACD tubes
C1D1	Plasma	ctDNA	1 x 10 ml EDTA tubes
C1D1	Whole blood	DNA	1 x 6 ml EDTA tube
C1D1	Whole blood	CTCs	2 x 10 ml Streck tubes
C2D1	Plasma	ctDNA	1 x 10 ml EDTA tubes
C2D1	Whole blood	CTCs	2 x 10 ml Streck tubes
C3D1	PBMCs	T-cells	3 x 8.5 ml ACD tubes
C3D1	Plasma	ctDNA	1 x 10 ml EDTA tubes
C3D1	Whole blood	CTCs	2 x 10 ml Streck tubes
C8D1	PBMCs	T-cells	3 x 8.5 ml ACD tubes
C8D1	Plasma	ctDNA	1 x 10 ml EDTA tubes
C8D1	Whole blood	CTCs	2 x 10 ml Streck tubes
Progression/safety	PBMCs	T-Cells	3 x 8.5 ACD tubes
Progression/safety	Plasma	ctDNA	1 x 10 ml EDTA tubes

8. BIOSPECIMEN STUDIES AND PROCEDURES

Tumor tissue, peripheral blood, and possibly normal urothelium will be used for biospecimen-based research in this study. The schedule of biospecimen collection(s), and ensure this schedule is reconciled with the Study Calendar. Full details of specimen collection and processing can be found in the CLM.

Correlative studies will include genomic sequencing of tumor tissue and/or peripheral blood and immune monitoring studies including T cell receptor sequencing and flow cytometry and/or mass cytometry on tissue and/or peripheral blood, antigen-specific T cell assays, HLA typing, and gene expression.

8.1 Tissue Samples

8.1.1 Archival Tissue

Representative formalin-fixed paraffin-embedded (FFPE) tumor specimens (metastatic specimens preferable but if not available primary tumor specimens that are at least muscle-invasive are acceptable) in paraffin blocks (blocks preferred) or at least 15 unstained slides. If archival tissue is not available, subjects may be considered for enrollment on a case by case basis after discussion with the sponsor-investigator. Samples will be utilized for studies including DNA sequencing, RNA sequencing, and characterization of the tumor and tumor microenvironment using existing and emerging technologies. Samples may also be stored for future cancer-related research. See Correlative Laboratory Manual (CLM) for additional details.

8.1.2 Tissue collected during routine clinical procedures

Surplus tissue remaining after routine standard of care procedures (e.g., metastatic biopsies) will be collected during this study. Subjects may have tumor tissue obtained during the course of the study or at the time of disease progression for clinical purposes (e.g., confirmation of disease progression, management of complication of disease progression, etc.). Specimens obtained in these settings may be accessed by the research team to facilitate an understanding of the pharmacodynamic effects of treatment at the level of the tumor and microenvironment including mechanisms of treatment resistance. Subjects will have the option of whether samples obtained during standard of care procedures may be used for research purposes.

8.1.3 Tissue Analysis

Analysis of tumor tissue may include assessment for changes in the composition of immune cells, tumor cells, and tumor microenvironment. Immune cell composition and changes in the tumor microenvironment will be analyzed by platforms including but not limited to immunohistochemistry, flow cytometry, and mass cytometry. An effort will be made to identify tumor antigens for each subject using strategies including, but not limited to, collating the "antigenome" using immunohistochemistry data as well as identifying mutation-derived tumor antigens through genome sequencing and computational biology approaches to predict epitope: MHC binding affinity. T-cell responses will be detected using standard ELISPOT and intracellular cytokine assays or other emerging technologies. DNA and RNA will be isolated for sequencing.

8.2 Whole Blood Samples

For blood samples, the volume of blood and type of tube to be used for each collection is specified in Table 4. Collection of blood samples is mandatory for participation in this study.

8.2.1 PBMCs for Immune Cell Analysis

The quantity and composition of immune cells in the peripheral blood mononuclear cells will be analyzed and clonality of T cells may also be assessed. Antigen specific T cell responses may also be detected as described above.

8.2.2 Plasma for ctDNA and other analyses

Plasma DNA will be isolated and analyzed for quantitative expression using sequence specific primers and/or for exome sequencing, cytokines/chemokines, and other analytes.

8.2.3 Circulating Tumor Cells Analysis

Whole blood samples will be collected to isolate circulating tumor cells which will then be used to evaluate changes in the quantity of circulating tumor cells as well as the expression of a variety of circulating tumor cell-based biomarkers.

8.2.4 Baseline Testing

Whole blood samples for germline DNA sequencing as a reference for somatic tissue DNA sequencing will be collected prior to treatment C1D1. HLA typing may also be performed for neoantigen predictions and other correlative analyses. See CLM for additional details.

8.3 Storage of Biospecimens

Excess biospecimens not completely utilized in these experiments will be stored indefinitely at HCRN for future use in research focused on GU malignant diseases that are yet to be determined. All specimens collected will maintain the assigned unique study number of the corresponding patient. Coded samples may be shared with other research institutions. We believe that allowing for storage and usage of the remaining samples for future research is ethically justified and a preferred option to discarding these materials given the potential impact on improving clinical outcomes for subjects with bladder cancer. Subjects will be given the option to store excess specimens during the informed consent process.

8.4 Confidentiality of Biospecimens

Samples that are collected will be identified by a subject's study number assigned at the time of registration to the trial. Any material issued to collaborating researchers will be anonymized and only identified by the subject's study number.

9. CRITERIA FOR DISEASE EVALUATION

9.1 Measurable Disease

Measurable disease is defined as the presence of at least one measurable lesion. Measurable lesions are defined as those that can be accurately measured in at least one dimension (longest diameter to be recorded) as $\geq$20 mm by chest x-ray, as $\geq$10 mm with CT scan, or $\geq$10 mm with calipers by clinical exam. All tumor measurements must be recorded in millimeters (or decimal fractions of centimeters).

9.1.1 Malignant Lymph Nodes

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

9.2 Non-measurable Lesions

All other lesions (or sites of disease), including small lesions (longest diameter <10 mm or pathological lymph nodes with ≥ 10 to <15 mm short axis), are considered non-measurable disease. Bone lesions, leptomeningeal disease, ascites, pleural/pericardial effusions, lymphangitis cutis/pulmonitis, inflammatory breast disease, and abdominal masses (not followed by CT or MRI), are considered as non-measurable.

NOTE: Cystic lesions that meet the criteria for radiographically defined simple cysts should not be considered as malignant lesions (neither measurable nor non-measurable) since they are, by definition, simple cysts. 'Cystic lesions' thought to represent cystic metastases can be considered as measurable lesions, if they meet the definition of measurability described above. However, if non-cystic lesions are present in the same subject, these are preferred for selection as target lesions.

9.3 Target Lesions

All measurable lesions up to a maximum of 2 lesions per organ and 5 lesions in total, representative of all involved organs, should be identified as target lesions and recorded and measured at baseline. Target lesions should be selected on the basis of their size (lesions with the longest diameter), be representative of all involved organs, but in addition should be those that lend themselves to reproducible repeated measurements. It may be the case that, on occasion, the largest lesion does not lend itself to reproducible measurement in which circumstance the next largest lesion which can be measured reproducibly should be selected. A sum of the diameters (longest for non-nodal lesions, short axis for nodal lesions) for all target lesions will be calculated and reported as the baseline sum diameters. If lymph nodes are to be included in the sum, then only the short axis is added into the sum. The baseline sum diameters will be used as reference to further characterize any objective tumor regression in the measurable dimension of the disease.

9.4 Non-target Lesions

All other lesions (or sites of disease) including any measurable lesions over and above the 5 target lesions should be identified as non-target lesions and should also be recorded at baseline. Measurements of these lesions are not required, but the presence, absence, or in rare cases unequivocal progression of each should be noted throughout follow-up.

9.5 Evaluation of Target Lesions

NOTE: In addition to the information below, also see section 4.3.2 in the international criteria proposed by the Response Evaluation Criteria in Solid Tumors (RECIST) Committee, version 1.1 (Eur J Cancer 45;2009:228-247) for special notes on the assessment of target lesions.

Complete Response (CR)	Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to <10 mm.
Partial Response (PR)	At least a 30% decrease in the sum of the diameters of target lesions, taking as reference the baseline sum diameters
Progressive Disease (PD)	At least a 20% increase in the sum of the diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. (Note: the appearance of one or more new lesions is also considered progressions).
Stable Disease (SD)	Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum diameters while on study

9.6 Evaluation of Non-Target Lesions

Complete Response (CR)	Disappearance of all non-target lesions and normalization of tumor marker level. All lymph nodes must be non-pathological in size (<10 mm short axis) Note: If tumor markers are initially above the upper normal limit, they must normalize for a subject to be considered in complete clinical response.
Non-CR/ Non-PD	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. Unequivocal progression should not normally trump target lesion status. It must be representative of overall disease status change, not a single lesion increase.

Although a clear progression of "non-target" lesions only is exceptional, the opinion of the site investigator should prevail in such circumstances, and the progression status should be confirmed at a later time by the sponsor investigator.

9.7 Evaluation of Best Overall Response

Target Lesions	Non-Target Lesions	New Lesions	Overall Response
CR	CR	No	CR
CR	Non-CR/ Non-PD	No	PR
CR	Not evaluated	No	PR
PR	Non-PD/ or not all evaluated	No	PR
SD	Non-PD or not all evaluated	No	SD
Not all evaluated	Non-PD	No	Non-evaluable
PD	Any	Yes or No	PD
Any	PD*	Yes or No	PD
Any	Any	Yes	PD
*In exceptional circumstances, unequivocal progression in non-target lesions may be accepted as disease progression.			

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

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

9.8 Definitions for Response Evaluation – RECIST 1.1

9.8.1 First Documentation of Response
The time between randomization and first documentation of PR or CR.

9.8.2 Duration of Response
Duration of overall response—the period measured from the time that measurement criteria are met for complete or partial response (whichever status is recorded first) until the date that recurrent or progressive disease is objectively documented (taking as reference for progressive disease the smallest measurements recorded since treatment started).

9.8.3 Duration of Overall Complete Response
The period measured from the time that measurement criteria are met for complete response until the first date that recurrent disease is objectively documented.

9.8.4 Objective Response Rate
The objective response rate is the proportion of all subjects with confirmed PR or CR according to RECIST 1.1, from the time of randomization until disease progression/recurrence (taking as reference for progressive disease the smallest measurements recorded since treatment initiation.

9.8.5 Disease Control Rate
The disease control rate is the proportion of all subjects with stable disease (SD) for 8 weeks, or partial response (PR), or complete response (CR) according to RECIST 1.1, from the time of randomization until disease progression/recurrence (taking as reference for progressive disease the smallest measurements recorded since the start of treatment).

9.8.6 Time to Progression
A measurement from the date of randomization until the criteria for disease progression is met as defined by RECIST 1.1. Subjects who have not progressed or have died due to any cause will be right-censored at the date of the last disease evaluation or date of death.

9.8.7 Progression Free Survival
A measurement from the date of randomization until the criteria for disease progression is met as defined by RECIST 1.1 or death occurs. Subjects who have not progressed will be right-censored at the date of the last disease evaluation.

9.8.8 Overall Survival
Overall survival is defined by the date of randomization to date of death from any cause.

10. DRUG INFORMATION

10.1 Nivolumab
Nivolumab is an anti-PD1 antibody. Nivolumab is a soluble protein consisting of 4 polypeptide chains, which include 2 identical heavy chains and 2 identical light chains.

Other Names Nivolumab, BMS-936558, MDX1106, anti-PD-1
Molecular Wt 146,221 daltons (143,619.17 daltons, protein portion)
Appearance Clear to opalescent, colorless to pale yellow liquid, few particulates may be present
Solution pH 5.5 to 6.5

10.1.1 Supplier/How Supplied
Nivolumab Injection, 100 mg/10 mL (10 mg/mL)

BMS will supply nivolumab at no charge to subjects participating in this clinical trial.

The site investigator shall take responsibility for and shall take all steps to maintain appropriate records and ensure appropriate supply, storage, handling, distribution, and usage of investigational product in accordance with the protocol and any applicable laws and regulations.

10.1.2 Preparation
Nivolumab Injection, 100 mg/10 mL (10 mg/mL)
Nivolumab injection is to be administered as an IV infusion through a 0.2-micron to 1.2-micro pore size, low-protein binding in-line filter at the protocol-specified doses and infusion times. It is not to be administered as an IV push or bolus injection. Nivolumab injection can be infused undiluted (10 mg/mL) or diluted with 0.9% Sodium Chloride Injection, USP or 5% Dextrose

Injection, USP to protein concentrations as low as 0.35 mg/mL. When the dose is fixed (eg, 240 mg flat dose), nivolumab injection can be infused undiluted or diluted so as not to exceed a total infusion volume of 120 mL. During drug product preparation and handling, vigorous mixing or shaking is to be avoided. Instructions for dilution and infusion of nivolumab injection may be provided in the clinical protocol, pharmacy binder, or pharmacy reference sheet. Care must be taken to assure sterility of the prepared solution as the product does not contain any antimicrobial preservative or bacteriostatic agent. No incompatibilities between nivolumab and polyvinyl chloride (PVC) and non-PVC/non-DEHP (di(2-ethylhexyl)phthalate) containers/IV components or glass bottles have been observed.

Nivolumab will be administered as an IV 30-minute infusion and should be administered prior to any other chemotherapy for the trial with at least a 30-minute period between nivolumab administration and the next chemotherapy.

10.1.3 Storage and Stability

Nivolumab Injection, 100 mg/10 mL (10 mg/mL)
Vials of nivolumab injection must be stored at 2° to 8°C (36° to 46°F) and protected from light and freezing.

Undiluted Nivolumab Injection and Diluted Nivolumab Injection in the IV Container.
The administration of nivolumab infusion must be completed within 24 hours of preparation. If not used immediately, the infusion solution may be stored under refrigeration conditions (2°to 8°C, 36°to 46°F) for up to 24 hours, and a maximum of 8 hours of the total 24 hours can be at room temperature (20° to 25°C, 68° to 77°F) and room light. The maximum 8-hour period under room temperature and room light conditions includes the product administration period.
After final drug reconciliation, unused nivolumab vials should be disposed at the site following procedures for the disposal of anticancer drugs.

10.1.4 Handling and Disposal

Preparation should be performed by trained personnel in accordance with good practices rules, especially with respect to asepsis.

A copy of the drug destruction certificate must be maintained to provide to BMS as documentation at the end of the study.

10.1.5 Dispensing

Nivolumab must be dispensed only from official study sites and to eligible subjects under the supervision of the site investigator. Nivolumab should be stored in a secure area according to local regulations. It is the responsibility of the site investigator to ensure that study drug is only dispensed to subjects.

10.1.6 Adverse Events

The most common side effects of nivolumab are:

- Fatigue
- Skin reactions: including rash, itching, hives, redness, and dry skin. Toxic epidermal necrolysis, a potentially life threatening disease characterized by blistering and peeling of the top layer of skin resembling that of a severe burn.
- Diarrhea
- Nausea
- Abdominal pain
- Decreased appetite
- Low red blood cells
- Fever
- Joint pain or stiffness

Less common side effects of nivolumab include:

- Bowel inflammation
- Liver function blood test abnormalities
- Loss of color (pigment) from areas of skin
- Dry mouth
- Vomiting
- Weight loss
- Thyroid gland abnormalities
- Blood chemistry abnormalities, including low blood phosphate, magnesium, and potassium levels.
- High blood uric acid level
- Lung inflammation (pneumonitis - see details below)
- Cough
- Dizziness
- Headache
- Low white blood cells
- Chills
- Muscle soreness, weakness, stiffness spasms or paralysis
- Pain in arms or legs
- Tingling, burning, or numbness in hands and feet
- Shortness of breath
- Abnormal taste
- Flushing
- High or low blood pressure
- Allergic reaction during or between study drug infusions
- Increased sensitivity of skin to sunlight
- Constipation
- Difficulty swallowing
- Heartburn
- Low blood platelets (may increase risk of bleeding)

Rare but potentially serious side effects of nivolumab include:

- Low blood oxygen level
- Acute lung injury or failure
- Collection of fluid around the lungs
- Inflammation of the appendix
- Increase in inflammatory blood proteins (e.g., lipase)
- Adrenal gland abnormalities
- Pituitary gland inflammation
- Changes in vision (including decreased or blurry vision), inflammation of the eye, or bleeding into the eye
- Liver inflammation
- Acute kidney injury or failure
- Abnormal blood cell production
- Inflammation of the mouth and lining of the digestive tract
- Swelling of the face, arms, or legs
- Inflammation of the pancreas
- Back pain
- Autoimmune disorders, including Guillain-Barre syndrome (associated with progressive muscle weakness or paralysis)
- Chest discomfort
- Heart palpitations
- Inflammation of the heart or its lining
- Collection of fluid around the heart
- Increased blood sugar
- Dehydration
- Infections: including sepsis, lung infections, and skin infections.
- Decreased movement of the intestines
- Disorientation
- Swelling of the optic disc
- Inflammation of the optic nerve
- Inflammation or loss of the lining of the brain and spinal cord
- Drug reaction with rash, blood cell abnormalities, enlarged lymph nodes, and internal organ involvement (including liver, kidney, and lung); known as Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS)
- Myasthenia gravis, a nerve disease that may cause weakness of eye, face, breathing, and swallowing muscles. One death in a patient who received nivolumab combined with ipilimumab was considered due to myasthenia gravis and severe infection (sepsis).
- Abnormal brain function due to brain inflammation.
- Rhabdomyolysis (muscle fiber released into the blood stream which could damage your kidney) and polymyositis (chronic muscle inflammation with muscle weakness) has been reported in one subject.
- Lung inflammation or pneumonitis

10.2 Gemcitabine

Please see product package insert for complete details regarding gemcitabine.

10.2.1. Chemical Name

1" – Deoxy – 2, 2" – difluorocytidine monohydrochloride, Gemzar, NSC #613327

10.2.2 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-potentiation). 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).

10.2.3 Availability

Gemcitabine is commercially available.

10.2.4 Storage, Reconstitution, and Administration

Storage, Reconstitution, and Administration as per institutional guidelines

10.2.5 Side Effects

Hematologic: In studies in pancreatic cancer, myelosuppression is the dose-limiting toxicity with gemcitabine, 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 Gemcitabine 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: Gemcitabine 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 gemcitabine or with greater total cumulative dose. Serious hepatotoxicity, including liver failure and death, has been reported very rarely in patients receiving gemcitabine alone or in combination with other potentially hepatotoxic drugs.

Renal: In clinical trials, mild proteinuria and hematuria were commonly reported. Clinical findings consistent with the Hemolytic Uremic Syndrome (HUS) were reported in 6 of 2429 patients (0.25%) receiving gemcitabine in clinical trials. Four patients developed HUS on Gemcitabine therapy, 2 immediately posttherapy. The diagnosis of HUS should be considered if the patient develops anemia with evidence of microangiopathic hemolysis, elevation of bilirubin or LDH, reticulocytosis, severe thrombocytopenia, and/or evidence of renal failure (elevation of serum creatinine or BUN). Gemcitabine therapy should be discontinued immediately. Renal failure may not be reversible even with discontinuation of therapy and dialysis may be required.

Fever: The overall incidence of fever was 41%. This is in contrast to the incidence of infection (16%) and indicates that gemcitabine 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 gemcitabine therapy. Dyspnea was occasionally accompanied by bronchospasm. Pulmonary toxicity has been reported with the use of gemcitabine (see Pulmonary under Post-marketing experience, below). The etiology of these effects is unknown. If such effects develop, Gemcitabine 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.

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

Allergic: Bronchospasm was reported for less than 2% of patients. Anaphylactoid reaction has been reported rarely. Gemcitabine should not be administered to patients with a known hypersensitivity to this drug.

Cardiovascular: During clinical trials, 2% of patients discontinued therapy with gemcitabine 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 gemcitabine. These events have occurred after gemcitabine single-agent use and gemcitabine 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 gemcitabine.

Cardiovascular – Congestive heart failure and myocardial infarction have been reported very rarely with the use of gemcitabine. 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 gemcitabine 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 gemcitabine administered to patients with various malignancies. Some patients experienced the onset of pulmonary symptoms up to 2 weeks after the last gemcitabine 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 gemcitabine. Renal failure leading to death 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. Gemcitabine 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/m^2 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/m^2 basis). Embryotoxicity was characterized by decreased fetal viability, reduced live litter sizes, and developmental delays. There are no studies of gemcitabine in pregnant women. If gemcitabine is used during pregnancy, or if the patient becomes pregnant while taking gemcitabine, the patient should be apprised of the potential hazard to the fetus.

Nursing mothers. It is not known whether Gemcitabine 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 gemcitabine 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.

10.3 Carboplatin
Please see product package insert for complete details regarding carboplatin.

10.3.1 Availability
Carboplatin is commercially available

10.3.2 Chemical Name
Platinum diamine [1,1-cyclobutane- decarbozxylate (2—0,0')-,(SP-4-2)]) is a platinum compound used as a chemotherapeutic agent.

10.3.3 Formulation
Carboplatin is available as a sterile lyophilized powder in single-dose vials containing 50 mg, 150 mg, or 450 mg of carboplatin. Each vial contains equal parts by weight of carboplatin and mannitol. Commercial supplies of carboplatin will be used in this study.

10.3.4 Availability
Carboplatin is commercially available.

10.3.5 Storage, Preparation, and Administration
Per Institutional guidelines.

10.3.6 Adverse Events Associated with Carboplatin
Incidence rates of adverse events associated with carboplatin are provided in the product package insert. Some of the adverse events expected with Carboplatin treatment are listed below.

Hematologic: Myelosuppression is the major dose-limiting toxicity. Thrombocytopenia, neutropenia, leukopenia, and anemia are common, but typically resolve by Day 28 when carboplatin is given as a single agent.

Allergic Reactions: Hypersensitivity to carboplatin has been reported in 2% of subjects receiving the drug. Symptoms include rash, urticaria, erythema, pruritus, and rarely bronchospasm and hypotension. The reactions can be successfully managed with standard epinephrine, corticosteroid, and antihistamine therapy.

Neurologic: Peripheral neuropathies have been observed in 4% of subjects receiving carboplatin with mild paresthesia being the most common.

Gastrointestinal: Nausea and vomiting are the most common GI events; both usually resolve within 24 hours and respond to antiemetics. Other GI events include diarrhea, weight loss, constipation, and gastrointestinal pain.
Hepatic Toxicity: Elevated alkaline phosphatase, total bilirubin, and SGOT have been observed.

Other: Pain and asthenia are the most common miscellaneous adverse events. Alopecia has been reported in 3% of the subjects taking carboplatin.

10.4 Oxaliplatin
Please see product package insert for complete details regarding oxaliplatin

10.4.1 Availability
Oxaliplatin will be paid for by the study.

10.4.2 Chemical name
cis-[(1 R,2 R)-1,2-cyclohexanediamine-N,N'] [oxalato(2)-O,O'] platinum

10.4.3 Storage, Preparation, and Administration
Per institutional guidelines

10.4.4 Adverse Events
For a comprehensive list of adverse events please refer to the package insert for oxaliplatin

- Central nervous system: Peripheral neuropathy, fatigue, pain, headache, insomnia, rigors, dizziness.
- Cardiovascular: Edema, chest pain, peripheral edema, flushing, thromboembolism.
- Gastrointestinal: Nausea, diarrhea, vomiting, abdominal pain, constipation, anorexia, stomatitis, dyspepsia, dysgeusia, flatulence, hiccups, mucositis, gastroesophageal reflux disease, dysphagia.
- Hematologic & oncologic: Anemia, thrombocytopenia, leukopenia, neutropenia.
- Hepatic: Increased serum AST, increased serum ALT, increased serum bilirubin.
- Endocrine & metabolic: Dehydration, hypokalemia.
- Neuromuscular & skeletal: Back pain, arthralgia.
- Respiratory: Dyspnea, cough, upper respiratory tract infection, rhinitis, epistaxis, pharyngitis, pharyngolaryngeal dysesthesia.
- Renal: Increased serum creatinine
- Dermatologic: Skin rash, alopecia, palmar-plantar erythrodysesthesia

- Hypersensitivity: Hypersensitivity reaction (includes urticaria, pruritus, facial flushing, shortness of breath, bronchospasm, diaphoresis, hypotension, syncope)
- Local: Injection site reaction
- Ocular: Abnormal lacrimation
- Miscellaneous: Fever

11 ADVERSE EVENTS

The descriptions and grading scales found in the NCI CTCAE v4 will be utilized for AE assessment. A copy of the CTCAE v4 can be downloaded from the CTEP website at http://ctep.cancer.gov.

11.1 Definitions

11.1.1 Adverse Event (AE)

An AE is any untoward medical occurrence whether or not considered related to the study drug that appears to change in intensity during the course of the study. The following are examples of AEs:

- Unintended or unfavorable sign or symptom
- A disease temporally associated with participation in the protocol
- An intercurrent illness or injury that impairs the well-being of the subject

Abnormal laboratory values or diagnostic test results constitute AEs only if they induce clinical signs or symptoms or require treatment or further diagnostic tests

Hospitalization for elective surgery or routine clinical procedures that are not the result of an AE (e.g., surgical insertion of central line) should not be recorded as an AE.
Disease progression should not be recorded as an AE, unless it is attributable to the study regimen by the site investigator.

11.1.2 Serious Adverse Event (SAE)

An SAE is an adverse event that:

- Results in death. **NOTE:** Death due to disease progression should not be reported as a SAE, unless it is attributable by the site investigator to the study drug(s)
- Is life-threatening (defined as an event in which the subject 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 for >24 hours or prolongation of existing hospitalization. **NOTE:** Hospitalization for anticipated or protocol specified procedures such as administration of chemotherapy, central line insertion, metastasis interventional therapy, resection of primary tumor, or elective surgery, will not be considered serious adverse events.
- 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 subject 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

For this study, an AE is considered unexpected when it varies in nature, intensity or frequency from information provided in the current IB, prescribing information or when it is not included in the informed consent document as a potential risk. Unexpected also refers to AEs that are mentioned in the IB as occurring with a class of drugs or are anticipated from the pharmacological properties of the drug, but are not specifically mentioned as occurring with the particular drug under investigation.

11.1.4 Relatedness

AEs will be categorized according to the likelihood that they are related to the study drug(s). Specifically, they will be categorized using the following terms:

Unrelated	Adverse Event is ***not related*** to the study drug(s)
Unlikely	Adverse Event is ***doubtfully related*** to the study drug(s)
Possible	Adverse Event ***may be related*** to the study drug(s)
Probable	Adverse Event is ***likely related*** to the study drug(s)
Definite	Adverse Event is ***clearly related*** to the study drug(s)

11.2 Reporting

11.2.1 Adverse Events

- AEs will be recorded from time of signed informed consent until 30 days after discontinuation of study drug(s) or until a new anti-cancer treatment starts, whichever occurs first.
- AEs will be recorded regardless of whether or not they are considered related to the study drug(s).
- All AEs will be recorded in the subject's medical record and on the appropriate study specific eCRF form within the EDC system.
- AEs considered related to study drug(s) will be followed until resolution to $\leq$ Grade 1 or baseline, deemed clinically insignificant, and/or until a new anti-cancer treatment starts, whichever occurs first.
- Transient asymptomatic laboratory abnormalities that do not require treatment will not be collected as adverse events.

11.2.2 Serious Adverse Events (SAEs)

11.2.2.1 Site Requirements for Reporting SAEs to HCRN

- SAEs will be reported from time of signed informed consent until 100 days after discontinuation of study drug(s) or until a new anti-cancer treatment starts, whichever occurs first.
- SAEs will be reported on the SAE Submission Form **within 1 business day** of discovery of the event.
- SAEs include events related and unrelated to the study drug(s).
- All SAEs will be recorded in the subject's medical record and on the appropriate study specific eCRF form within the EDC system.
- All SAEs regardless of relation to study drug will be followed until resolution to ≤ Grade 1 or baseline and/or deemed clinically insignificant and/or until a new anti-cancer treatment starts, whichever occurs first.

The site will submit the completed SAE Submission Form to HCRN **within 1 business day** of discovery of the event**.** The form may be submitted to HCRN electronically to safety@hoosiercancer.org. The site investigator is responsible for informing the IRB and/or other local regulatory bodies as per local requirements. The original copy of the SAE Submission Form and the email correspondence must be kept within the study file at the study site.

Once the SAE has resolved (see resolution guidelines listed in 11.2.2.1), sites must submit a follow-up SAE Submission Form within a reasonable timeframe to HCRN electronically to safety@hoosiercancer.org.

HCRN will ensure that all SAEs are reported to BMS and any applicable health authority during the conduct of the study including periodic reconciliation. SAEs need to be reconciled every 3 months by HCRN initiating the reconciliation activity with BMS by emailing AEBUSINESSPROCESS@BMS.com and including this information on the regular study status update reports.

11.2.2.2 HCRN Requirements for Reporting SAEs to Bristol-Myers Squibb Company

HCRN will report all SAEs to BMS **within 1 business day** of receipt of the SAE Submission Form from a site. Follow-up information will be provided to BMS as it is received from site.

HCRN will submit all SAEs to BMS Global Pharmacovigilance (GPV&E) via email @ worldwide.safety@bms.com or fax @ 609-818-3804.

11.2.2.3 Sponsor-Investigator Responsibilities

HCRN will send a SAE summary to the sponsor-investigator **within 1 business day** of receipt of SAE Submission Form from a site. The sponsor-investigator will promptly review the SAE summary and assess for expectedness and relatedness.

11.2.2.4 HCRN Responsibilities to FDA

HCRN will manage the Investigational New Drug Application (IND) associated with this protocol on behalf of the sponsor-investigator. HCRN will cross-reference this submission to the Bristol-Myers Squibb's parent IND at the time of submission. Additionally, HCRN will submit a copy of these documents to Bristol-Myers Squibb's at the time of submission to FDA.

For protocols conducted under an IND, HCRN will be responsible for all communication with the FDA in accordance with 21CFR312 including but not limited to the 7 and 15 Day Reports, as well as an Annual Progress Report. Additionally, HCRN will submit a copy of these reports to Bristol-Myers Squibb's at the time of submission to FDA.

11.2.2.5 IND Safety Reports Unrelated to this Trial

Bristol-Myers Squibb's will provide to HCRN IND safety reports from external studies that involve the study drug(s) per their guidelines. HCRN will forward safety reports to the sponsor-investigator who will review these reports and determine if revisions are needed to the protocol or consent. HCRN will forward these reports to participating sites **within 1 business day** of receiving the sponsor-investigator's review. Based on the sponsor-investigator's review, applicable changes will be made to the protocol and informed consent document (if required). All IND safety reports will also be made available to sites via the EDC system.

Upon receipt from HCRN, site investigators (or designees) are responsible for submitting these safety reports to their respective IRBs, as per their IRB policies.

12 STATISTICAL METHODS

12.1 Study Design

This is a randomized, open-labeled phase 2 trial of gemcitabine + carboplatin + nivolumab or gemcitabine + oxaliplatin + nivolumab for the treatment of cisplatin-ineligible patients with metastatic urothelial cancer. Randomization will be stratified on the lymph node only (and/or unresectable primary) metastatic status.

12.2 Endpoints

12.2.1 Definition of Primary Endpoint

- Response rate as determined by RECIST v1.1

12.2.2 Definition of Secondary Endpoints

- Safety will be determined according to the NCI Common Terminology Criteria for Adverse Events (NCI CTCAE) v4
- Duration of response will be the time from the first documentation of RECIST 1.1 response to the time of progression as per RECIST 1.1.
- Progression-free survival which is defined as the time from randomization to death or progression, depending on which occurs first
- Overall survival is defined as the time from randomization to death

12.3 Sample Size and Accrual

A randomized phase 2 'pick a winner design' will be employed.[1] Two regimens are to be studied and the expected baseline response rate is ~40%. With 21 patients per arm, we have probability 0.9 of selecting the regimen that has a true response rate of 40%+20%=60% [or, allows selection of the regimen that is 18% better (in terms of response rate) than the other regimen with 0.88 probability and 15% better with 0.83 probability]. We will inflate the sample size on each study arm to account for early drop-outs/unevaluable patients to ~24 patients per arm. Because our randomization is stratified on the lymph node (LN) only (and/or unresectable primary) metastasis status, we further calculate the probability of correctly selecting the better treatment, similar to the Table 3 in Simon et al. (1985) [1]. In particular, we assume that approximately 30% of patients will have LN only metastasis. Response rate can be as high as 60% for this particular group. The probabilities of correctly selecting the better treatment are listed in the table below assuming the response rate for the LN only metastasis range from 50% to 60%. The overall response rate is fixed at 40%. We can see that these probabilities are satisfactory and do not seem to be substantially impacted by the stratification.

Probabilities of Correctly Selecting the Better Treatment based on n=22 per Arm

		Improvement in response rate for the other metastasis group		
		20%	**18%**	**15%**
		Using 50% as the response rate of the LN only group		
Improvement in response rate for the lymph node only metastasis group	**20%**	0.911	0.895	0.868
	18%	0.903	0.887	0.858
	15%	0.891	0.873	0.843
		Using 55% as the response rate of the LN only group		
	20%	0.913	0.898	0.871
	18%	0.906	0.889	0.861
	15%	0.893	0.876	0.845
		Using 60% as the response rate of the LN only group		
	20%	0.917	0.902	0.876
	18%	0.909	0.893	0.865
	15%	0.897	0.879	0.849

12.4 Data Analysis Plans

12.4.1 Analysis Plans for Primary Objective

All subjects who have received at least one cycle of treatment and have their disease re-evaluated will be evaluable for assessment of the response rate. The objective response rate (PR + CR) and its associated 95% confidence interval will be constructed. Comparison between the two treatments will be conducted using the Fisher's exact test. Difference will be estimated using the exact method.

12.4.2 Analysis Plans for Secondary Objectives

Any subject who receives at least one dose of treatment on this protocol is evaluable for toxicity. Toxicity rates will be summarized using frequency tables. Comparison between the treatments will be conducted using the Fisher's exact test. Time to event outcomes (i.e. Duration of response, progression-free survival, and overall survival) will be analyzed using the Kaplan-Meier method. Comparison between the treatments will be conducted using the log-rank test.

12.4.3 Analysis Plans for Exploratory Objectives

The effects of treatment on peripheral blood biomarkers of immune modulation and immunogenic cell death will be estimated using difference of pre- and post-treatment measurements. Association of these markers (i.e. their changes) with the response will be explored using t-tests. Their association with the time-to-event clinical outcomes will be explored using the Cox proportional hazards model. Model assumptions will be checked and if violated, other models will be attempted. Similar analyses will be conducted for the tumor tissue biomarkers based on a subset of patients (5 patients per arm). However, the small sample size may prohibit formal statistical analysis. Impact of somatic mutations, including DNA damage response gene alterations on response rate will be conducted using Fisher's exact test. Their impact on the time-to-event outcomes will be explored using the log-rank test. Antigen-specific T cell responses in peripheral blood (pre-treatment vs. post-treatment) will be analyzed using t-tests.

12.5 Interim Analysis/Criteria for Stopping Study

The stopping rule will be employed separately for the two arms after 7, 14, and 21 subjects finish at least one cycle of treatment. Therefore, it is possible to stop one arm and continue the other arm. Two-sided 95% exact binomial confidence intervals (CIs) of these grade ≥ 3 immune-related adverse event rates will be constructed.

When the trial was initially designed, there were no large datasets in urothelial cancer of platinum-based chemotherapy plus PD-1/PD-L1 blockade and limited published studies with PD-1/PD-L1 blockade in urothelial cancer in the first-line setting. Based on the datasets available at the time, the study was designed such that if the lower bounds of the 95% CI for grade ≥ 3 immune-related adverse event rate exceeded 3% for either arm, that regimen would be considered to be associated with excessive toxicity and enrollment to that arm would be halted. However, during the conduct of the current study, two large randomized trials exploring platinum-based chemotherapy versus platinum-based chemotherapy plus PD-1/PD-L1 blockade versus PD-1/PD-L1 blockade have been published provided much more robust data on which to base the grade ≥ 3 immune-related adverse event rate with PD-1/PD-L1 blockade alone in this patient population as well as with platinum-based chemotherapy plus PD-1/PD-L1 blockade in this patient population. There data are summarized in the tables below.

From KEYNOTE 361 (Powles et al, Lancet Oncology, 2021)[22]

Table S7: Immune-mediated adverse events in the as-treated population.*

Event	Pembrolizumab + Chemotherapy (N = 349)		Pembrolizumab (N = 302)		Chemotherapy (N = 342)	
	Any Grade	Grade 3-5	Any Grade	Grade 3-5	Any Grade	Grade 3-5
Hypothyroidism	35 (10%)	2 (1%)	30 (10%)	1 (<1%)	1 (<1%)	0
Pneumonitis	14 (4%)	3 (1%)	13 (4%)	4 (1%)	2 (1%)	1 (<1%)
Hyperthyroidism	14 (4%)	1 (<1%)	10 (3%)	0	0	0
Severe skin reactions	10 (3%)	8 (2%)	5 (2%)	2 (1%)	3 (1%)	2 (1%)
Adrenal insufficiency	6 (2%)	1 (<1%)	1 (<1%)	0	0	0
Colitis	4 (1%)	2 (1%)	5 (2%)	4 (1%)	2 (1%)	1 (<1%)
Hypophysitis	3 (1%)	3 (1%)	2 (1%)	1 (<1%)	0	0
Thyroiditis	3 (1%)	0	3 (1%)	1 (<1%)	0	0
Myositis	3 (1%)	0	2 (1%)	0	0	0
Pancreatitis	2 (1%)	2 (1%)	2 (1%)	2 (1%)	0	0
Myocarditis	2 (1%)	1 (<1%)	0	0	0	0
Hepatitis	1 (<1%)	1 (<1%)	2 (1%)	1 (<1%)	0	0
Nephritis	1 (<1%)	1 (<1%)	1 (<1%)	1 (<1%)	0	0
Type 1 diabetes mellitus	1 (<1%)	1 (<1%)	1 (<1%)	1 (<1%)	0	0
Sarcoidosis	1 (<1%)	0	0	0	0	0
Encephalitis	0	0	1 (<1%)	1 (<1%)	0	0

Infusion-related reactions occurred in 8 patients (2%; all grade 1-2) in the pembrolizumab plus chemotherapy arm, 3 patients (1%; including one grade 3-4 event) in the pembrolizumab arm, and 4 patients (1%; including one grade 3-4 event) in the chemotherapy arm. *As-treated population includes all patients who received ≥1 dose of trial treatment.

IMvigor 130 (Galsky et al, Lancet, 2020[23]; see AEs of special interest)

	Group A (n=453)	Group B (n=354)	Group C (n=390)
Total deaths	236 (52%)	190 (54%)	223 (57%)
Adverse events regardless of attribution			
Any grade adverse events	451 (>99%)	329 (93%)	386 (99%)
Grade 3 or 4 adverse events	383 (85%)	148 (42%)	334 (86%)
Grade 5 adverse events	29 (6%)	28 (8%)	20 (5%)
Treatment-related adverse events	434 (96%)	211 (60%)	373 (96%)
Treatment-related grade 3 or 4 adverse events	367 (81%)	54 (15%)	315 (81%)
Treatment-related grade 5 adverse events	9 (2%)	3 (1%)	4 (1%)
Serious adverse events			
Regardless of attribution	234 (52%)	152 (43%)	191 (49%)
Treatment-related serious adverse events	144 (32%)	44 (12%)	101 (26%)
Adverse events leading to any treatment discontinuation	156 (34%)	22 (6%)	132 (34%)
Adverse events leading to discontinuation of atezolizumab or placebo	50 (11%)	21 (6%)	27 (7%)
Adverse events leading to discontinuation of cisplatin	53 (12%)	0	52 (13%)
Adverse events leading to discontinuation of carboplatin	90 (20%)	1 (<1%)*	79 (20%)
Adverse events leading to discontinuation of gemcitabine	117 (26%)	1 (<1%)*	100 (26%)
Adverse events leading to any dose reduction or interruption	363 (80%)	112 (32%)	304 (78%)
Any grade adverse events of special interest	227 (50%)	132 (37%)	135 (35%)
Grade 3 or 4 adverse events of special interest	34 (8%)	29 (8%)	17 (4%)
Grade 5 adverse events of special interest	3 (1%)	2 (1%)	1 (<1%)

Data are n (%). *This patient was randomly assigned to group A and received atezolizumab; they had an adverse event of pyrexia that day, and gemcitabine and carboplatin were marked as drug withdrawn. Since no chemotherapy was given, this patient was included in group B for safety analysis.

Table 3: **Safety summary**

Arm A = platinum-based chemotherapy plus atezolizumab, Arm B = atezolizumab, Arm C = platinum-based chemotherapy

Based on these large randomized trials in patients with metastatic urothelial cancer, the grade ≥ 3 immune-related adverse event rate with PD-1/PD-L1 blockade alone or with platinum-based chemotherapy plus PD-1/PD-L1 blockade is ~9%. Based on these findings, in the current study, if the lower bound of the 95% CI for the grade ≥ 3 immune-related adverse events exceeds 9% for either arm, the study regimen being explored in that arm will be considered to have excessive toxicity and enrollment to that arm will be halted. This corresponds to ≥ 3+ (3 or more) out of 7, ≥ 5+ (5 or more) out of 14, and ≥ 6+ out of 21 subjects.

13 TRIAL MANAGEMENT

13.1 Data and Safety Monitoring Plan (DSMP)

The study will be conducted with guidance from the Icahn School of Medicine/Tisch Cancer Institute's DSMP

HCRN oversight activities include:

- Review and processing of all adverse events requiring expedited reporting as defined in the protocol
- Provide trial accrual progress, safety information and data summary reports to the sponsor-investigator
- Submit data summary reports to the DSMC for review.

13.2 Tisch Cancer Institute Cancer Center Data Safety Monitoring Committee

HCRN will provide the following for the DSMC to review:

- Adverse event summary report
- Audit results, if applicable
- Data related to stopping/decision rules described in study design
- Study accrual patterns
- Protocol deviations

The DSMC will review study data at least every 6 months. Documentation of DSMC reviews will be provided to sponsor-investigator and HCRN. Issues of immediate concern by the DSMC will brought to the attention of the sponsor-investigator and other regulatory bodies as appropriate. The sponsor-investigator will work with HCRN to address the DSMC's concerns.

13.3 Data Quality Oversight Activities

Remote validation of the EDC system data will be completed on a continual basis throughout the life cycle of the study. Automated edit check listings will be used to generate queries in the EDC system and transmitted to the site to address in a timely fashion. Corrections will be made by the study site personnel.

Participating sites may also be subject to quality assurance audits as well as inspection by appropriate regulatory agencies.

13.3.1 Onsite Monitoring

Monitoring visits to the trial sites may be made periodically during the trial to ensure key aspects of the protocol are followed. Additional for cause visits may occur as necessary. Selected source documents will be reviewed for verification of agreement with data entered into the EDC system. It is important for the site investigator and their relevant personnel to be available for a sufficient amount of time during the monitoring visits or audit, if applicable. The site investigator and institution guarantee access to source documents by HCRN or its designee.

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

13.4 Compliance with Trial Registration and Results Posting Requirements

Under the terms of the Food and Drug Administration Modernization Act (FDAMA) and the Food and Drug Administration Amendments Act (FDAAA), the sponsor-investigator of the trial is solely responsible for determining whether the trial and its results are subject to the requirements for submission to the Clinical Trials Data Bank, http://www.clinicaltrials.gov. All results of primary and secondary objectives must be posted to CT.gov within a year of completion. The sponsor-investigator has delegated responsibility to HCRN for registering the trial and posting the results on clinicaltrials.gov. Information posted will allow subjects to identify potentially appropriate trials for their disease conditions and pursue participation by calling a central contact number for further information on appropriate trial locations and study site contact information.

13. DATA HANDLING AND RECORD KEEPING

14.1 Data Management

HCRN will serve as the Clinical Research Organization for this trial. Data will be collected through a web based clinical research platform, a system compliant with Good Clinical Practices and Federal Rules and Regulations. HCRN personnel will coordinate and manage data for quality control assurance and integrity. All data will be collected and entered into the EDC system by study site personnel from participating institutions.

14.2 Case Report Forms and Submission

Generally, clinical data will be electronically captured in the EDC system and correlative results will be captured in the EDC system or other secure database(s). If procedures on the study calendar are performed for standard of care, at minimum, that data will be captured in the source document. Select standard of care data will also be captured in the EDC system, according to study-specific objectives.

The completed dataset is the sole property of the sponsor-investigator's institution and should not be exported to third parties, except for authorized representatives of appropriate Health/Regulatory Authorities, without permission from the sponsor-investigator and HCRN.

14.3 Record Retention

To enable evaluations and/or audits from Health Authorities/HCRN, the site investigator agrees to keep records, including the identity of all subjects (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. All source documents are to remain in the subject's file and retained by the site investigator in compliance with the site contract with HCRN. No records will be destroyed until HCRN confirms destruction is permitted.

14.4 Confidentiality

There is a slight risk of loss of confidentiality of subject information. All records identifying the subjects will be kept confidential and, to the extent permitted by the applicable laws and/or regulations, will not be made publicly available. Information collected will be maintained on secure, password protected electronic systems. Paper files that contain personal information will be kept in locked and secure locations only accessible to the study site personnel.

Subjects will be informed in writing that some organizations including the sponsor-investigator and his/her research associates, HCRN, Bristol-Myers Squibb's, IRB, or government agencies, like the FDA, may inspect their medical records to verify the information collected, and that all personal information made available for inspection will be handled in strictest confidence and in accordance with local data protection laws.

If the results of the study are published, the subject's identity will remain confidential.

15 ETHICS

15.1 Institutional Review Board (IRB) Approval

The final study protocol and the final version of the informed consent form must be approved in writing by an IRB. The site investigator must submit written approval by the IRB to HCRN before he or she can enroll subjects into the study.

The site 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 subjects for the study. The protocol must be re-approved by the IRB, as local regulations require.

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

15.2 Ethical Conduct of the Study

The study will be performed in accordance with ethical principles originating from the Declaration of Helsinki. Conduct of the study will be in compliance with ICH Good Clinical Practice, and with all applicable federal (including 21 CFR parts 56 & 50), state, or local laws.

15.3 Informed Consent Process

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

The subject's signed and dated informed consent must be obtained before conducting any procedure specifically for the study. The site investigator must store the original, signed informed consent form. A copy of the signed informed consent form must be given to the subject.

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APPENDIX A: AE MANAGEMENT ALGORITHMS

GI Adverse Event Management Algorithm

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

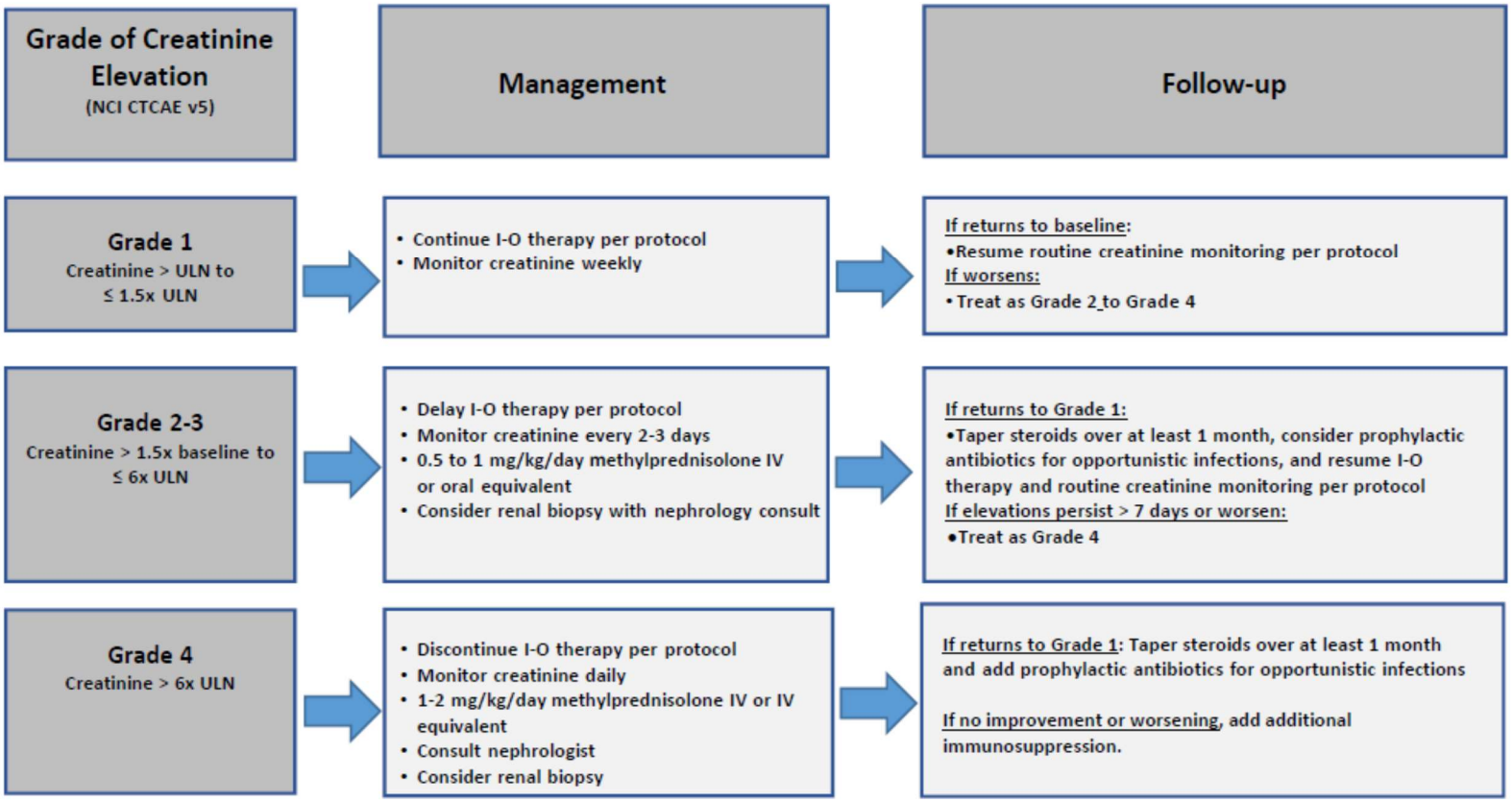
Grade of Diarrhea/ Colitis (NCI CTCAE v5)	Management	Follow-up
Grade 1 Diarrhea: < 4 stools/day over baseline Colitis: asymptomatic	• Continue I-O therapy per protocol • Symptomatic treatment	• Close monitoring for worsening symptoms • Educate patient to report worsening immediately If worsens: • Treat as Grade 2 or Grade 3-4
Grade 2 Diarrhea: 4-6 stools per day over baseline; IV fluids indicated < 24 hrs; Limiting instrumental ADL Colitis: abdominal pain; blood in stool	• Delay I-O therapy per protocol • Symptomatic treatment	If improves to Grade 1: • Resume I-O therapy per protocol If persists > 5-7 days or recurs: • 0.5-1 mg/kg/day methylprednisolone or oral equivalent • When symptoms improve to Grade 1, taper steroids over at least 1 month, consider prophylactic antibiotics for opportunistic infections, and resume I-O therapy per protocol. If worsens or persists > 3-5 days with oral steroids: • Treat as Grade 3-4
Grade 3-4 Diarrhea (G3): ≥ 7 stools per day over baseline; IV fluids ≥24 hrs; limiting self care ADL Colitis (G3): severe abdominal pain, peritoneal signs G4: life-threatening, perforation	• Discontinue or delay I-O therapy per protocol* • 1 to 2 mg/kg/day methylprednisolone IV or IV equivalent • Add prophylactic antibiotics for opportunistic infections • Consider lower endoscopy	If improves: • Continue steroids until grade 1, then taper over at least 1 month If persists > 3-5 days, or recurs after improvement: • Add infliximab 5 mg/kg (if no contraindication) or other immunosuppressants. • Consider testing CMV for steroid refractory colitis Note: Infliximab should not be used in cases of perforation or sepsis

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

* Discontinue for Grade 4 diarrhea or colitis. For Grade 3 diarrhea or colitis, 1) Nivolumab monotherapy: Nivolumab can be delayed. 2) Nivolumab+ Ipilimumab combination: Ipilimumab should be discontinued while nivolumab can be delayed. Nivolumab monotherapy can be resumed when symptoms improve to Grade 1. Please refer to protocol for dose delay and discontinue criteria for other combinations.

Renal Adverse Event Management Algorithm

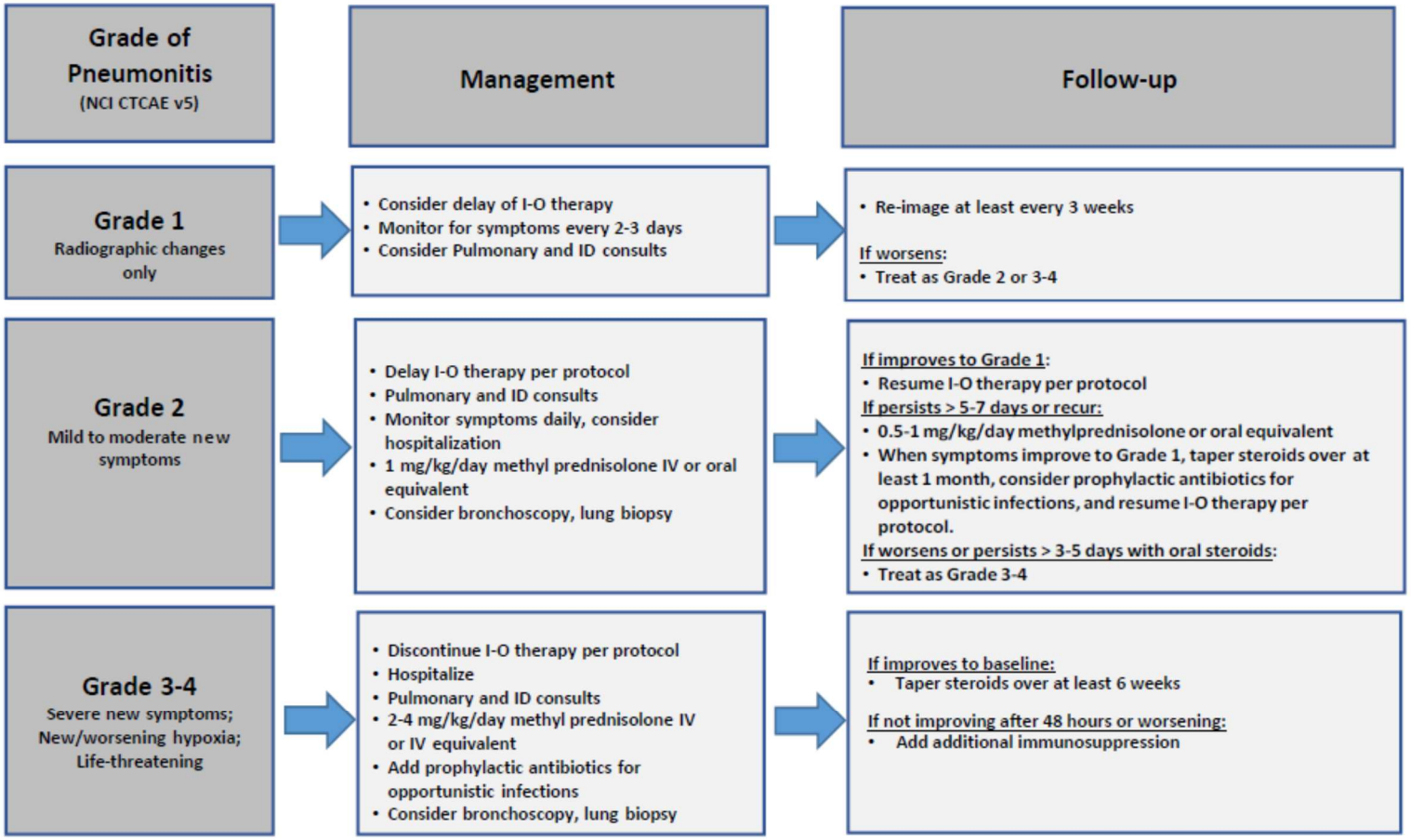
Rule out non-inflammatory causes. If non-inflammatory cause, treat accordingly and continue I-O therapy.



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

Pulmonary Adverse Event Management Algorithm

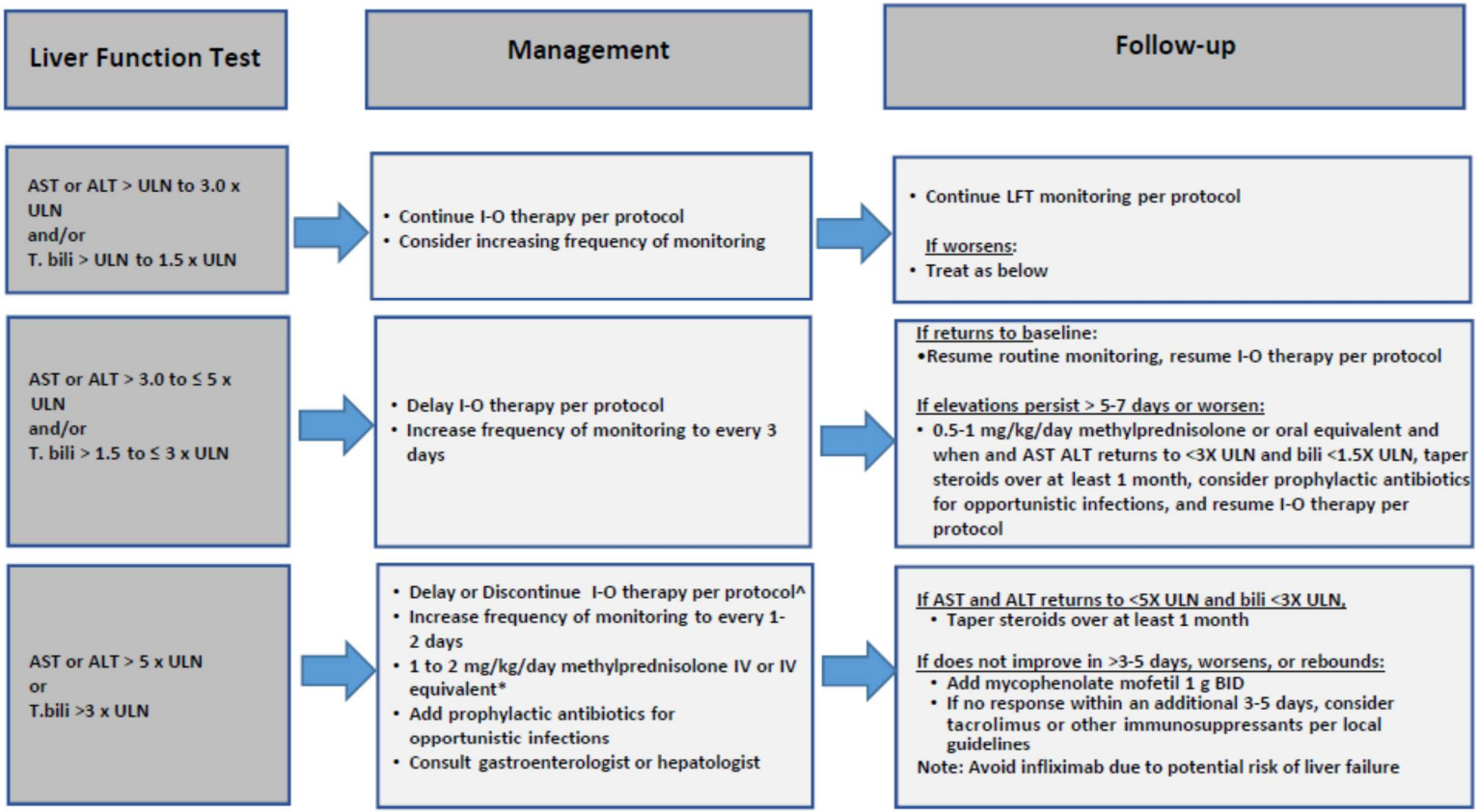
Rule out non-inflammatory causes. If non-inflammatory cause, treat accordingly and continue I-O therapy.
Evaluate with imaging and pulmonary consultation.



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

Hepatic Adverse Event Management Algorithm

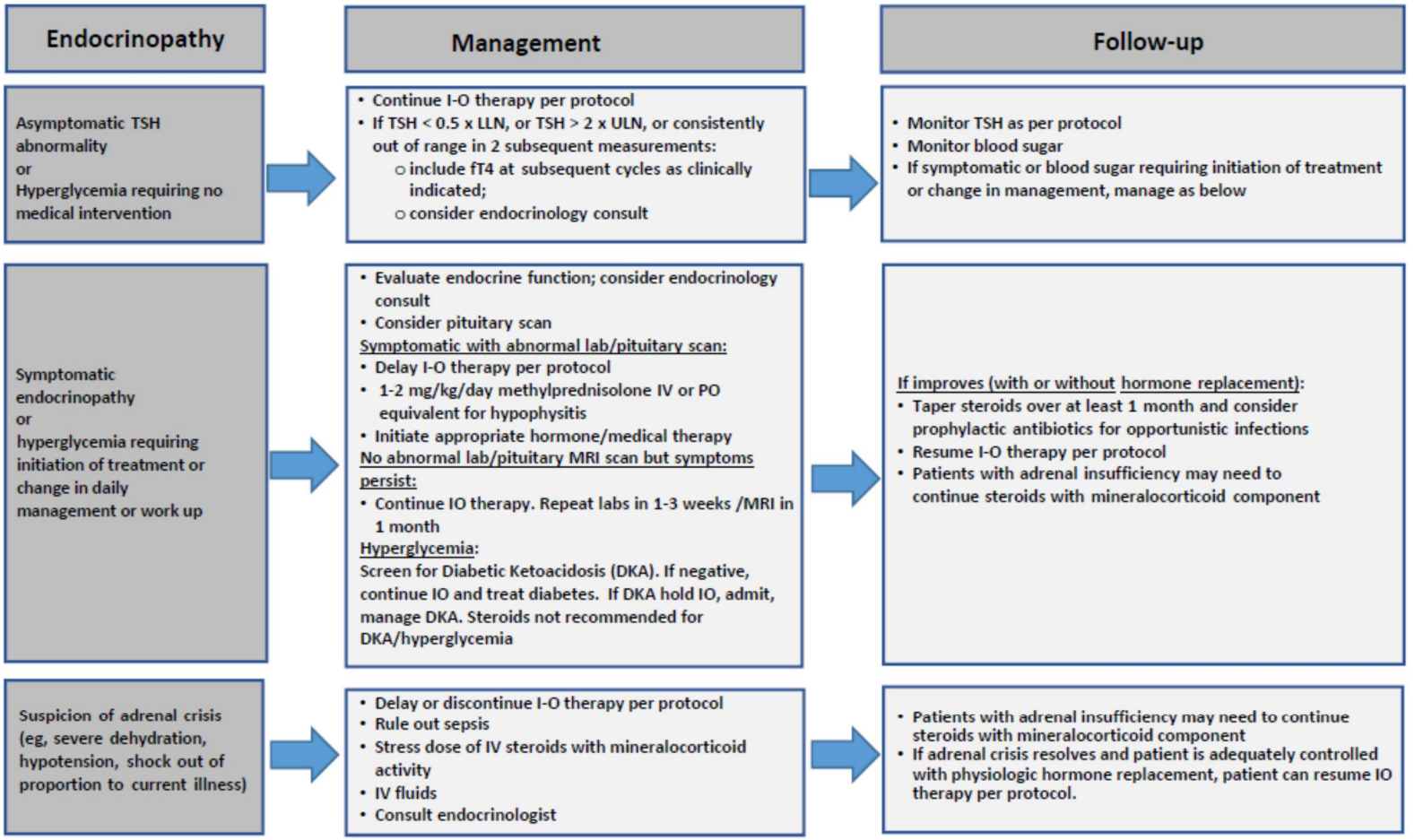
Rule out non-inflammatory causes. If non-inflammatory cause, treat accordingly and continue I-O therapy.
Consider imaging for obstruction.



Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, after sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of oral corticosteroids.
^ Please refer to protocol dose delay and discontinue criteria for specific details.
*The recommended starting dose for AST or ALT > 20 x ULN or bilirubin >10 x ULN is 2 mg/kg/day methylprednisolone IV.

Endocrinopathy Adverse Event Management Algorithm

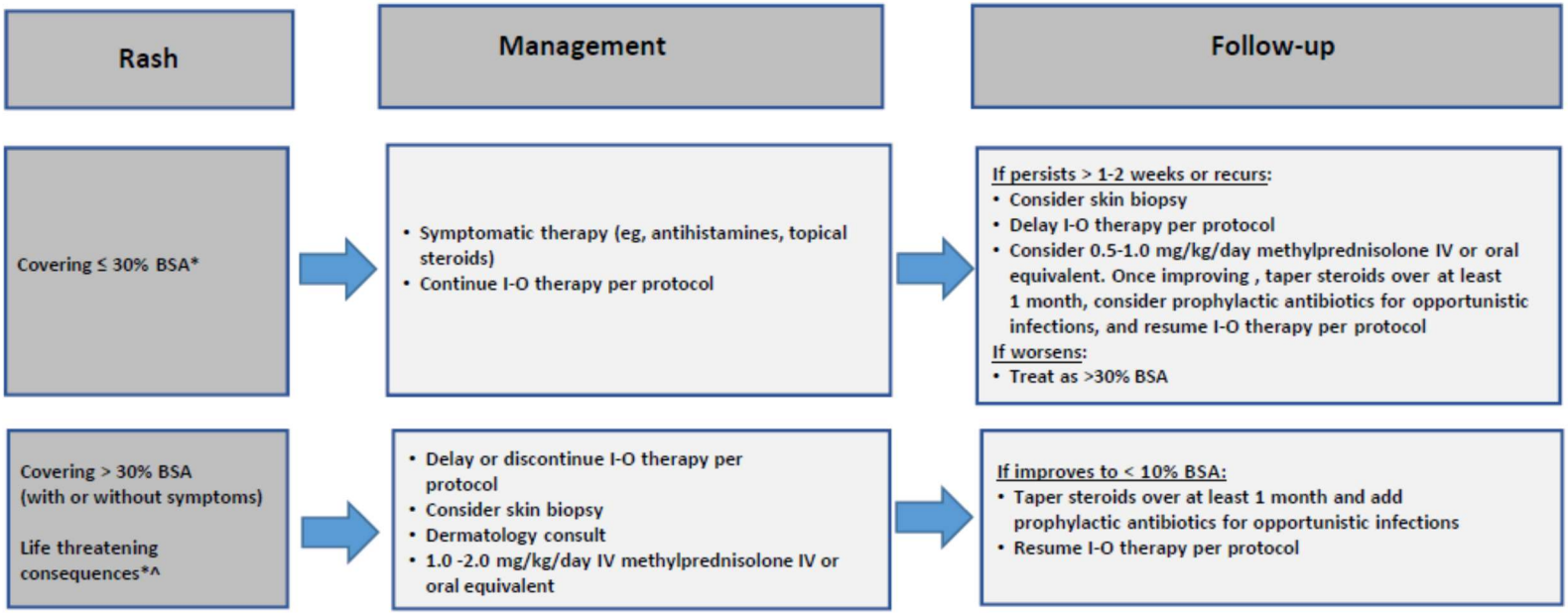
Rule out non-inflammatory causes. If non-inflammatory cause, treat accordingly and continue I-O therapy.
Consider visual field testing, endocrinology consultation, and imaging.



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

Skin Adverse Event Management Algorithm

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



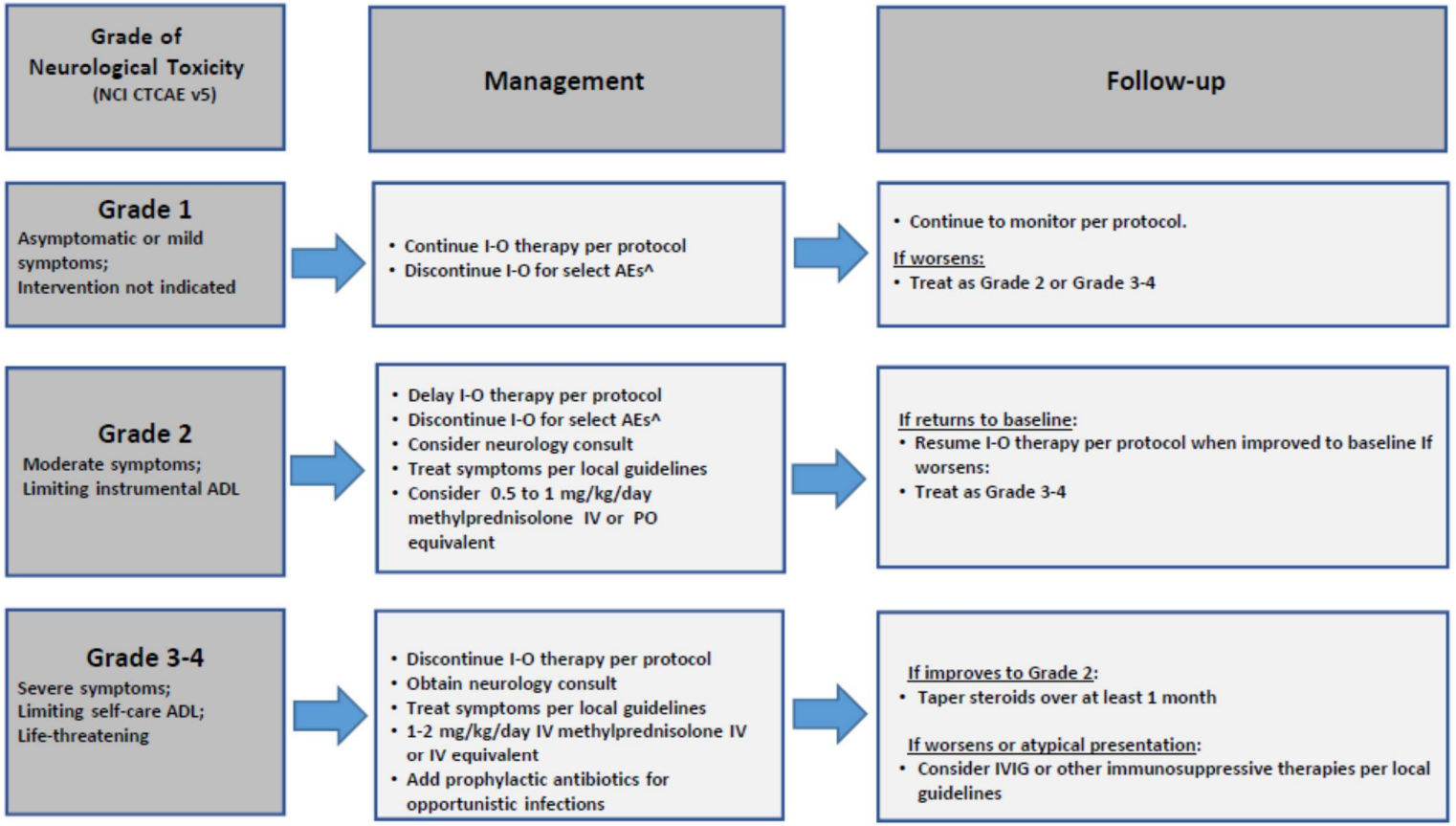
Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, after sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of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

*Refer to NCI CTCAE v5 for term-specific grading criteria.

^If Steven-Johnson Syndrome (SJS),toxic epidermal necrosis (TEN), Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS) is suspected, withhold I-O therapy and refer patient for specialized care for assessment and treatment. If SJS, TEN, or DRESS is diagnosed, permanently discontinue I-O therapy.

Neurological Adverse Event Management Algorithm

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

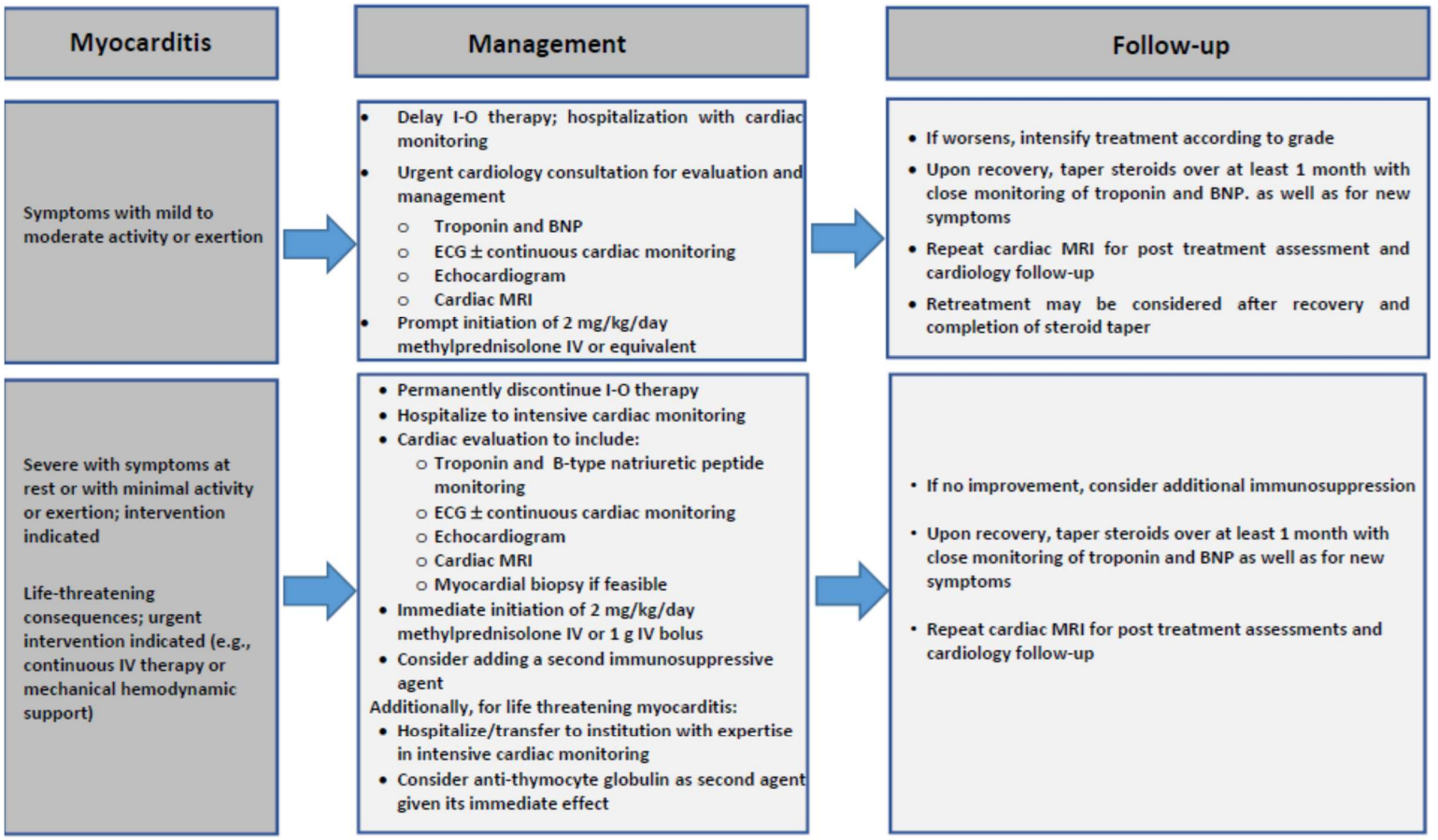


Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (eg. prednisone) at start of tapering or earlier, after sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of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

^Discontinue for any grade myasthenia gravis, Guillain-Barre syndrome, treatment-related myelitis, or encephalitis.

Myocarditis Adverse Event Management Algorithm

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



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

Prophylactic antibiotics should be considered in the setting of ongoing immunosuppression.