**KCI Protocol # 2016-195**

# Phase II Trial of Concurrent Nivolumab in UroThelial Bladder Cancer with Radiation Therapy in Localized/Locally Advanced Disease for Chemotherapy Ineligible Patients [NUTRA]

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**Phase II Trial of Concurrent Nivolumab in Urothelial Bladder Cancer with Radiation Therapy in Localized /Locally Advanced Disease for Chemotherapy Ineligible Patients [NUTRA]**

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**SYNOPSIS**

**Phase II Trial of Concurrent Nivolumab in Urothelial Bladder Cancer with Radiation Therapy in Localized/Locally Advanced Disease for Chemotherapy Ineligible Patients [NUTRA]**

- **Primary Objective:**

  To compare the 12-month rate of progression-free (PFS) survival achieved with the combination of nivolumab, a programmed death (PD-1) inhibitor, and radiation therapy in localized/locally advanced urothelial cancer patients, who are ineligible for chemotherapy, to a historical control reference rate.

- **Secondary Objectives:**

  1) To assess the toxicity of concurrent nivolumab and radiation therapy in urothelial cancer.
  2) To determine overall response rate (ORR).
  3) To determine metastasis-free survival (MFS).
  4) To determine overall survival (OS).
  5) To evaluate the quality of life and bladder functioning during and after the therapy.
  6) To explore the relationships of PD-1 expression, PDL-1 expression, and the Th1/Th2 cytokine ratio to clinical outcomes (response, PFS, MFS, and OS).

- **Treatment Plan:**

  - Nivolumab will be administered at a dose of 240 mg IV every 2 weeks for a maximum of 14 doses or 6 months duration.
  - Radiation Therapy (RT) needs to be started within +/- 3 days of nivolumab administration. RT would be administered at a total dose of 64 Gy in 32 fractions over a 6-8 week period in all patients.

- **Study Assessments:**

  Prestudy evaluation, CT/MRI scan, cystoscopy and biopsy, and archival tissue. Clinical and lab evaluation on day of nivolumab therapy. QOL assessment at the 15 time points listed in the header of the Study Calendar in Section 2.3.

- **Statistical Design:**

Sample size based on an assumed 12 month PFS rate of 50% on RT alone currently and a hypothesized rate of 75% for Nivolumab + RT study patients. A total of 34 patients are to

be accrued to get 30 evaluable for PFS. Evaluable for PFS and toxicity evaluable have the same definition (in Section 4.7).

## 1.0 BACKGROUND AND RATIONALE

### 1.1 Study Objectives

The objectives of this study are as follows:

- Primary Objective:

To compare the 12-month rate of progression-free survival (PFS) achieved with the combination of nivolumab, a programmed death (PD-1) inhibitor, and radiation therapy in localized/locally advanced urothelial cancer patients, who are chemotherapy ineligible, to a historical control reference 12-month PFS rate.

- Secondary Objectives:
  1) To assess the toxicity of concurrent nivolumab and radiation therapy in urothelial cancer.
  2) To determine overall response rate (ORR).
  3) To determine metastasis-free survival (MFS).
  4) To determine overall survival (OS).
  5) To evaluate the quality of life and bladder functioning during and after the therapy.
  6) To explore the relationships of PD-1 expression, PDL-1 expression, and the Th1/Th2 cytokine ratio to clinical outcomes (response, PFS, MFS, and OS).

### 1.2 Background

The standard management of localized urothelial cancer of bladder consists of neoadjuvant chemotherapy followed by radical cystectomy [1]. If patients wish to pursue a bladder sparing procedure then regimens of either 5FU and mitomycin, or cisplatin concurrently with radiation therapy (RT) are accepted therapeutic approaches [2]. However, these regimens are not feasible in a subset of bladder cancer patients who are ineligible for chemotherapy. Bladder cancer is a disease of the elderly and the incidence increases with increasing age. The median age of incidence of bladder cancer is 73 years and 9 of 10 cases occur in patients over the age of 55 years. In addition, the bladder cancer population has a very high rate of associated comorbidities such as renal dysfunction, cardiac and vascular disease and neuropathy which are frequently deterrents to administering chemotherapy. In

some series the patients who are not candidates for cisplatin based therapy due to comorbidities range up to about 40-50% of the patients presenting with localized disease. The morbidity of bladder cancer is frequently significant, with hematuria, urinary obstruction and renal dysfunction being the common and recurring complaints. Cisplatin based therapy concurrently with RT, has demonstrated results comparable to the surgical series; however, the toxicity rates are significant and about 40% of the patients are not candidates for chemotherapy [3,4]. A concurrent regimen of 5FU and mitomycin with RT [5] showed improved outcomes when compared to RT alone; however, the severe toxicity rates of 36% are a definite deterrent. We have reported on a case series of 13 patients receiving concurrent capecitabine and RT in localized bladder cancer, in whom we observed reasonable palliation and response rates [6]. 11 of 13 evaluable patients demonstrated a response and at a median follow up of 10 months only 3 had relapsed. The most common overall toxicities were fatigue (43%), diarrhea (Grade 2, 14% and Grade 3, 29%), and dehydration (43%), with no Grade 4 or 5 toxicities. The therapy options for treatment of symptomatic bladder cancer in patients who are ineligible for chemotherapy demonstrate suboptimal efficacy and hence there is an unmet need to improve the therapeutic outcomes within this patient population.

### 1.3 Nivolumab and Radiation Therapy (RT)

Nivolumab is a programmed death (PD) 1 inhibitor that has demonstrated safety and efficacy in multiple human malignancies and is currently approved by the FDA for the indications of metastatic melanoma, lung cancer, and renal cancer. A single arm phase II clinical trial in metastatic and post chemotherapy urothelial cancer population was completed and results were recently reported. The study showed a 19.6% (53 of 270 patients) overall response rate and a 25% response rate in patients with PDL-1 expression $\geq$1%. Some remissions are durable and follow up is continued. This data led to FDA approval of nivolumab in metastatic urothelial cancer post platinum based chemotherapy [7].

Preclinical synergy has been noted between nivolumab and RT in urothelial cancer. In fact the inflammation induced by the RT is likely to increase PD-1 expression in the cancer and will likely enhance efficacy. RT has shown the following effects in urothelial carcinoma: 1) increased CD8 cell function and increased cytokine release, 2) abscopal response in metastatic sites not being treated within the RT field, 3) the RT has been known to release tumor antigens and can convert the tumor into an in situ tumor vaccine, and 4) complementary and potentially synergistic effects in combination with immune checkpoint

inhibitors. In summary, association with proinflammatory signals that trigger the innate immune system to activate tumor-specific T cells, radiation's effects on the tumor microenvironment also enhance infiltration of activated T cells and enable overcoming some of the barriers to tumor rejection [8-11].

In the US, nivolumab has been approved for the treatment of patients with unresectable or metastatic melanoma and disease progression following ipilimumab and, if BRAF V600 mutation positive, a BRAF inhibitor. It has also been approved for use in patients with advanced (metastatic) squamous non-small cell lung cancer (NSCLC) with progression on or after platinum-based chemotherapy. Nivolumab was recently approved for metastatic urothelial cancer for patients with disease progression after platinum based chemotherapy.

Nivolumab monotherapy has been extensively studied in a number of tumor types including non-small cell lung cancer, melanoma, renal cancer, and head and neck cancer with body weight normalized dosing (mg/kg) [12]. Across the various tumor types in the Bristol-Myers Squibb (BMS) clinical program, nivolumab has been shown to be safe and well tolerated up to a dose level of 10 mg/kg, and the relationship between nivolumab exposure produced by 3 mg/kg and efficacy has been found to be unchanged at different dose levels. Taken together, the PK, safety, and efficacy data indicate that the safety and efficacy profile of 240 mg nivolumab will be similar to that of 3 mg/kg nivolumab.

Nivolumab has been evaluated in a phase II randomized trial at dose cohorts of 0.3mg/kg, 3mg/kg and 10mg/kg [13]. No differences were noted in safety and efficacy between each of these dose levels. BMS has tested and validated a flat dose regimen of 240 mg IV infusion of nivolumab every 2 weeks which is currently approved by FDA. Hence a flat dose is used in the study regardless of patient weight.

Nivolumab pharmacokinetics (PK) and exposures of subjects in these studies have been characterized by population pharmacokinetic (PPK) analysis of data collected these studies, together with PK data from several phase 1, 2, and 3 clinical studies of nivolumab monotherapy in solid tumors. PPK analyses have shown that the PK of nivolumab are linear, with dose proportional exposures over a dose range of 0.1 mg/kg to 10 mg/kg, and are similar across tumor types. Nivolumab clearance and volume of distribution were found to increase with increasing body weight, but the increase was less than proportional, indicating that a mg/kg dose represents an over-adjustment for the effect of body weight on nivolumab PK. Given the relationship between nivolumab PK and body weight, a flat

dose is expected to lead to lower exposures in heavier patients, relative to the exposures in lighter patients.

Using the PPK model, nivolumab steady-state trough, peak and time-averaged concentration (Cminss, Cmaxss, and Cavgss, respectively) were predicted for a flat nivolumab dose of 240 mg Q2W and compared to those following administration of 3 mg/kg Q2W in NSCLC subjects. A dose of 240 mg nivolumab is identical to a dose of 3 mg/kg for subjects weighing 80 kg, which is the approximate median body weight of NSCLC subjects in the 3 Phase 2 and 3 BMS clinical studies of nivolumab monotherapy. The geometric mean values of Cminss, Cmaxss, and Cavgss with flat dosing are slightly (< 15%) higher than that produced by a 3 mg/kg dose, and the coefficient of variation (cv%) in these measures of exposure are only slightly (< 10%) greater than that of 3 mg/kg dosing.

Thus a flat dose of 240 mg every 2 weeks is recommended for investigation in this study.

### 1.4 Risk Benefit Ratio of Proposed Regimen

The proposed study is specifically addressing an unmet need of treating bladder cancer in patients who are not candidates for chemotherapy. This is a growing subset of population within bladder cancer with increasing incidence in elderly patients with impaired performance status or renal function or associated comorbidities.

Also PD-1 inhibition therapy has demonstrated efficacy in urothelial cancer and nivolumab was recently FDA approved for use in urothelial cancer of bladder. The benefit risk ratio for the proposed study is very favorable as nivolumab is well tolerated and has proven efficacy in urothelial cancer. There is adequate clinical trial data establishing the role of nivolumab in urothelial cancer and the results have led to FDA approval for this indication. There are clinical trials conducted in lung cancer and melanoma evaluating the combination of nivolumab and RT with promising efficacy and established safety.

The standard therapy for patients who cannot tolerate a radical cystectomy procedure for localized/locally advanced bladder cancer is concurrent chemotherapy consisting of either cisplatin and 5FU or 5FU and mitomycin regimen with RT. However at least 40% of patients with bladder cancer are not candidates for chemotherapy but are likely to tolerate immune therapy. This study is proposed in the chemotherapy ineligible patient population for whom palliative care is radiation therapy alone. Adding concurrent nivolumab is likely to have radiosensitizing effect and enhance efficacy outcomes.

The majority of treatment and study procedures are routine therapy for treatment of bladder cancer. Nivolumab is being provided by BMS. The radiation therapy and labs are part of routine care. Scans for staging pre and post therapy are also part of routine care. The bladder surveillance with cystoscopy and biopsy after therapy completion are also considered routine therapy. Study related research procedures such as immune monitoring and correlative studies will be covered by the study funding.

### 1.5 Study Sites

Karmanos Cancer Institute, Detroit MI will be the coordinating center and will be joined by participating sites to open this trial. There will be about 2-3other subsites where this study will be open.

### 1.6 Withdrawals

Subjects may discontinue study treatment or withdraw their consent to participate in the study at any time without prejudice. The investigator may withdraw a subject from study treatment or from the study if, in his or her clinical judgment, it is in the best interest of the subject or if the subject cannot comply with the protocol.

In addition, any of the following conditions require withdrawal of the subject from study treatment:

- An AE or intercurrent illness that in the opinion of the investigator warrants the subject's withdrawal from treatment
- Necessity for treatment with other investigational drug or other anticancer medications prohibited by protocol
- Participation in another clinical study using an investigational agent
- Request by regulatory agencies for termination of treatment of an individual subject or all subjects under this protocol
- Sexually active subjects who refuse to use medically accepted barrier methods of contraception (e.g., male condom, or diaphragm with spermicidal gel) during the course of the study and for 3 months following discontinuation of study treatment.
- Inability to tolerate nivolumab

- Nivolumab treatment delays greater than 6 weeks
- Progressive disease (PD) as determined by the investigator.

The reason for study treatment discontinuation will be documented. For subjects who discontinue or are withdrawn from study treatment, every effort must be made to undertake protocol-specified follow-up procedures and end-of-treatment assessments, if possible, unless consent for follow up in the study is also withdrawn.

If a subject fails to return for the protocol-defined visits, an effort must be made to determine the reason. If the subject cannot be reached by telephone, a registered letter should be sent to the subject (or the subject's legal guardian) requesting contact with the clinic.

If a subject is discontinued from study treatment because of an AE considered to be related to study treatment and the event is ongoing 30 days after the last dose of study treatment, the event must be followed until resolution or determination by the investigator that the event has become stable or irreversible.

If a subject withdraws consent to participate in the study, the reason for withdrawal will be documented, no study procedures or assessments will be performed, and no further study data will be collected for this subject, other than the determination of survival status from public records such as government vital statistics or obituaries.

## 2.0 STUDY DESIGN

### 2.1 Nivolumab administration

Nivolumab will be administered at a flat dose of 240 mg IV infusion over 30 minutes +/- 10 minutes every 2 weeks for a maximum of 14 doses or 6 months duration. No premedications are required. If infusion reaction occurs, then premedications should be added with antihistamine, nonsteroidal anti-inflammatory drugs and/or steroids. Steroid therapy should be avoided if possible as premedication. The infusion should be given over 60-90 minutes +/- 10 minutes if infusion reaction occurs.

## 2.2 Radiation Therapy

Radiation Therapy (RT) needs to be started within +/- 3 days of nivolumab administration. Either therapy can be started first. RT would be administered at a total dose of 64 Gy in 32 fractions over a 6-8-week period in all patients. The RT can be done at any institution as it is Standard of Care and not covered by the study. The details of radiation therapy as required per protocol will be sent to the treating radiation oncologist.

SIMULATION

- Patient should be instructed to void prior to simulation for PTV40 to 46 Gy radiation course. Re-simulation with full bladder permissible for PTV64 Gy if bladder lesions can be visualized and adequately treated with daily IGRTCT simulation will be performed in the supine position with cradle immobilization recommended. Use of contrast is at the discretion of the treating radiation oncologist.

TECHNICAL FACTORS

- Radiotherapy will be delivered via linear accelerator with a minimum energy of 6 MV.
- Treatment will be delivered using either a three dimensional conformal approach (typically 3-4 field) or intensity modulated radiotherapy (IMRT) per institutional preference. Intensity modulated radiotherapy is only permissible if performed with daily CBCT or MVCT.

TREATMENT PLANNING

- Careful delineation of gross target volume ($GTV_{BLADDER}$) should be performed utilizing available imaging and bladder mapping to encompass all known areas of gross disease. For patients with radiographically or pathologically involved pelvic lymph nodes, a separate nodal GTV ($GTV_{NODE}$) should be defined.
- The clinical target volumes (CTV) will be delineated as follows:
    - $CTV_{PRIMARY} = GTV_{BLADDER}$
    - $CTV_{BLADDER}$: The entire bladder, including all gross intravesicular and extravesicular disease
    - $CTV_{NODE} = GTV_{NODE}$

- $CTV_{PELVIS}$: Inclusion of areas of potential microscopic spread, including external iliac, internal iliac, perivesical, presacral and obturator nodes, as well as, the prostate in male patients, is at the discretion of the treating physician. In the case of node positive disease, the pelvic lymph nodes should be included in the initial treatment field.

- The planning target volume (PTV) expansions are to be performed as follows:
  - $PTV_{BLADDER}$: 1.5 cm expansion around the bladder CTV
  - $PTV_{NODE}$: 0.5 to 1 cm expansion around radiographically or pathologically positive lymph node GTV
  - $PTV_{PELVIS}$: 0.5 to 1 cm expansion around the elective nodal CTV as defined above
  - $PTV_{40\ to\ 46\ Gy}$ is a Boolean of $PTV_{PELVIS} + PTV_{NODE} + PTV_{BLADDER} + PTV_{64\ Gy}$ .
  - $PTV_{54\ to\ 60\ Gy}$ is a Boolean of $PTV_{NODE} + PTV_{64\ Gy}$
  - Adjustment of the PTV to meet dose constraints is allowable at the discretion of the treating radiation oncologist. *If the treatment course is to be delivered in more than one phase, it is necessary to generate separate planning target volumes (e.g. $PTV_{BLADDER}$, $PTV_{NODE}$, etc) utilizing the PTV expansions as delineated above.*

- The total PTV64 Gy dose delivered will be 64 Gy in 2 Gy per fraction.

o 64 Gy Rx to cover at least 98% of PTV64 Gy

o Minimum dose within PTV64 Gy– 95% of prescribed dose and for a volume that is 0.03 cc

o Maximum dose within the PTV64 Gy – 110% of prescribed dose and for a volume that is 0.03 cc

- the initial phase of therapy will consist of a dose of 40 to 46 Gy delivered to PTVPELVIS, PTVNODE, and PTVBLADDER.
- The initial course of therapy should be delivered with an empty bladder and the boost should be delivered with a partial/full bladder.
- Radiation therapy may be delivered in up to three phases:

o Treatment to the pelvic lymph nodes is recommended; the initial phase of therapy will consist of a dose of 40 to 46 Gy delivered to PTVPELVIS, PTVNODE, and PTVBLADDER. The initial course of therapy should be delivered with an empty bladder

o The initial phase of therapy will consist of a dose of PTV40 to 46 Gy

- 40-46 Gy Rx to cover at least 98% of PTV40 to 46 Gy
- Minimum dose within PTV40 to 46 Gy – 95% of prescribed dose and for a volume that is 0.03 cc
- Maximum dose within the PTV40 to 46 Gy – 110% of prescribed dose and for a volume that is 0.03 cc

o For patients with positive nodal disease, a second phase of treatment will consist of a dose of 54 Gy to 60 Gy delivered to PTV54 to 60 Gy (Boolean of PTVNODE and PTV64 Gy.)

o The final phase of treatment will consist of a total dose of 64 Gy delivered to PTV64 Gy. In cases where the bladder GTV is readily discernible and daily IGRT with CB imaging is utilized, a partial bladder boost (PTV 64 Gy) for the final 5 treatments (10 Gy) is permissible at the discretion of the treating radiation oncologist.

- The total $PTV_{64\ Gy}$ delivered will be 64 Gy in 2 Gy per fraction.
  - 64 Gy Rx to cover at least 98% of $PTV_{64\ Gy}$
  - Minimum dose within $PTV_{64\ Gy}$– 95% of prescribed dose and for a volume that is 0.03 cc
  - Maximum dose within the $PTV_{64\ Gy}$ – 110% of prescribed dose and for a volume that is 0.03 cc

- Radiation therapy may be delivered in up to three phases:
  - The initial course of therapy should be delivered with an empty bladder
  - The initial phase of therapy will consist of a dose of $PTV_{40\ to\ 46\ Gy}$
    - 40-46 Gy Rx to cover at least 98% of $PTV_{40\ to\ 46\ Gy}$
    - Minimum dose within $PTV_{40\ to\ 46\ Gy}$ – 95% of prescribed dose and for a volume that is 0.03 cc
    - Maximum dose within the $PTV_{40\ to\ 46\ Gy}$ – 110% of prescribed dose and for a volume that is 0.03 cc
  - For patients with positive nodal disease, a second phase of treatment will consist of a dose of 54 Gy to 60 Gy delivered to $PTV_{54\ to\ 60\ Gy}$ (Boolean of $PTV_{NODE}$ and $PTV_{64\ Gy}$.)

- The final phase of treatment will consist of a total dose of 64 Gy delivered to $PTV_{64\ Gy}$. In cases where the bladder GTV is readily discernible and daily IGRT with CB imaging is utilized, a partial bladder boost ($PTV_{64\ Gy}$) for the final 5 treatments (10 Gy) is permissible at the discretion of the treating radiation oncologist. In this case, the patient may undergo a re-simulation with a full bladder at the discretion of the treating radiation oncologist.

CRITICAL STRUCTURES

- Bladder, rectum and femoral heads should be defined as organs at risk (OAR). Rectum should be defined from the anorectal ring caudally to the rectosigmoid junction cranially. The following dose constraints should be met:
  - Rectum V30 <50%
  - Rectum V55 <10%
  - Femoral heads Maximum dose limit <45 Gy per RTOG 0926
  - Small bowel and sigmoid. V30<30%, maximum dose limit 50 Gy.

## 2.3 Study Calendar

Prestudy labs, physical exam and EKG should be done within 28 days of day 1. Day 1 labs can be done within 3 days of day 1. A window of +/- 3 days is permitted for the days of nivolumab therapy.

| Testing | Pre study | Wk 1 | Wk 3 | Wk 5 | Wk 7 | Wk 9 | Wk 11 | Wk 13 | Wks 15,17, 19,21, 23,25 | 6, 9 and 12 mths[4] |
|---|---|---|---|---|---|---|---|---|---|---|
| H and P | X | X | X | X | X | X | X | X | X | X |
| VS, Wt | X | X | X | X | X | X | X | X | X | X |
| PS | X | X | X | X | X | X | X | X | X | X |
| Tox | X | X | X | X | X | X | X | X | X | X |
| Labs[1] | X | X | X | X | X | X | X | X | X | X |
| TSH, free T3/T4 | X | | | | X | | | X | | X |
| ECG[2] | X | | | | | | | | | |
| Cystoscopy[7] | X | | | | | | | X | | X |

| | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| Biopsy[7] | X | | | | | | | X | | X |
| CT/MRI[3] of abdomen/ pelvis | X | | | | | | | X | | X |
| CXR/ chest CT[3] | X | | | | | | | | | |
| Nivolumab | | X | X | X | X | X | X | X | X | |
| Visits during RT[5] | | X | X | X | X | X | | | | |
| PFS/OS[6] | | X | X | X | X | X | X | X | X | X |
| Biomarkers[3] | X | | | | X | | | X | | X |
| QOL questionnaires [3] | X | X | X | X | X | X | X | X | X | X |

1. Labs include: CBC diff, platelets, Electrolytes, BUN, creatinine, glucose, Albumin, alkaline phosphatase, total bilirubin, calcium, total protein, SGOT, SGPT. Pregnancy test for women of child bearing potential within 7 days of study enrollment and every 6 weeks thereafter.

2. ECG at screening and repeat if clinically indicated.

3. ICF, Baseline biomarkers, QOL questionaires and all tumor evaluation/measurement scans must be within 42 days prior to treatment. CT/MRI of abdomen and pelvis is required for pretreatment and subsequent tumor assessments. CXR/CT chest is required at screening only to evaluate for metastases. Biomarkers should be collected at time of PD.

4. 6, 9 and 12 month visits will be from start of therapy. A window of +/- 28 days is permitted for these visits.

5. RT will be done **continuously** daily Monday to Friday (except for weekends and holidays) for a total of 32-35 fractions from week 1 to week 8. The time period of 8 weeks is a maximum duration as the radiation fractions can get delayed due to holidays, machine downtime, patient cancellation due to transportation etc. During RT patients should be evaluated for toxicity at a minimum every other week. Nivolumab should be started +/- 3 days of first day of RT.

6. After 12 months the patients will be followed for PFS and OS every 3 months for a maximum of 5 years.

7. Screening cystoscopy and biopsy can be performed within 6 months of day 1. On study cystoscopy will be done at week 13 and at months 6, 9 and 12 +/- 28 days. Biopsies will be required at week 13, month 6 and month 12 +/- 28 days. Month 9 biopsies done if clinically indicated.
The 6, 9 and 12 month timepoints for cystoscopy and biopsy (if needed) are to be followed for patients with no e/o malignancy in the bladder and no e/o metastases.
For patients requiring intra-vesical therapy for residual/new T1 or CIS in bladder, treatment will proceed as per standard of care and no specified timepoints will be followed. However, results of cystoscopy and biopsy should continue to be collected.

## 3.0 STUDY POPULATION

### 3.1 Inclusion Criteria

1) Localized urothelial cancer of bladder with presence of transitional cell carcinoma (TCC) component. Mixed histologies are allowed.
2) Clinical or pathologic stage T2 –T4 disease including T4a and 4b if feasible to treat with radiation therapy.
3) Locoregional lymph node metastases are permitted but patients with distant metastases are ineligible. Imaging to evaluate for distant metastases should consist of a minimum of CT/MRI of abdomen/pelvis or CT urogram and a CXR or CT chest. Patients for which there is clinical suspicion or symptoms of bone metastasis should have a bone scan completed to rule out metastatic disease prior to enrollment on study.
4) Agreeable to consider radiation therapy (RT) for the urothelial cancer: patients have to be evaluated by a radiation oncologist and deemed to be candidates for RT.
5) The patients must not be candidates for chemotherapy due to at least one of the following reasons:
    a. Performance status of 2
    b. Creatinine clearance $\leq$ 60 ml/min as calculated by the Cockcroft-Gault formula.
    c. Cardiac disease such as NYHA Class III or IV heart failure or cardiac ischemia within the last 12 months, grade 2 or greater neuropathy, or other

comorbidities based on which patient is not considered a candidate for chemotherapy.

6) Adequate liver function with alkaline phosphatase, AST and ALT $\leq$3 x upper limit of normal and bilirubin < 1.5 x ULN
7) Adequate Bone marrow function defined as absolute neutrophil count $\geq$1500/mm$^3$ and hemoglobin $\geq$9 g/dL and platelets $\geq$ 100K/mm$^3$.
8) PS of 0-2 by Zubrod score
9) Life expectancy of 12 months
10) Age $\geq$18 years of age
11) Willingness to sign informed consent
12) Patients cannot have active autoimmune disease or immunosuppressive conditions.
13) Serum creatinine $\leq$ 1.5 X institutional ULN or creatinine clearance > 40 ml/min as calculated by the Cockcroft-Gault formula.
14) In females with childbearing potential, or men with partners of child bearing potential, willingness to use adequate contraception during the treatment period and for a minimum duration of 5 months after last dose of nivolumab.
15) Maximal tumor resection has been performed as feasible.

### 3.2 Exclusion Criteria

A subject who meets any of the following criteria is ineligible for the study:

1) The subject has received cytotoxic chemotherapy (including investigational cytotoxic chemotherapy) or biologic agents (e.g., cytokines or antibodies) for urothelial cancer within 4 weeks, or intravesical BCG within 6 weeks of the first dose of study treatment.
2) Prior treatment with any PD-1 or PDL-1 inhibitor
3) The subject has received therapeutic radiation:
    a. to the bladder/prostate/rectum pelvis
    b. to any other site(s) within 28 days of the first dose of study treatment
4) Obstructive renal failure that is not relieved with stents or nephrostomy tube/s.

5) The subject has received any other type of investigational agent within 28 days before the first dose of study treatment.

6) Steroid doses greater than an equivalent of prednisone 10 mg daily

7) Uncontrolled hematuria

8) The subject has uncontrolled, significant intercurrent or recent illness including, but not limited to, the following conditions:

    a. Cardiovascular disorders such as uncontrolled arrhythmias or uncontrolled congestive heart failure.

    b. Gastrointestinal disorders particularly those associated with a high risk of perforation or fistula formation including:

        i. Any of the following at the time of screening

            1. active peptic ulcer disease,

            2. active inflammatory bowel disease (including ulcerative colitis and Crohn's disease), diverticulitis, cholecystitis, symptomatic cholangitis or appendicitis

        ii. Any of the following within 6 months before the first dose of study treatment:

            1. history of abdominal fistula
            2. Bowel perforation

9) The subject has a previously identified allergy or hypersensitivity to components of the study treatment formulation.

10) The subject is unable or unwilling to abide by the study protocol or cooperate fully with the investigator or designee.

11) Presence of another invasive malignancy, which required systemic therapy within 12 months of protocol enrollment, except for resected skin cancers or prostate cancer that is in remission.

12) Pregnant or nursing women

13) Patient is a candidate for radical cystectomy as a potentially curative option. The patient may not be a candidate for radical cystectomy due to any of the following reasons: comorbidities, patient preference, or physician discretion.

14) Patients with inherited syndromes associated with hypersensitivity to ionizing radiation (e.g., Ataxia-Telangiectasia, Nijmegen Breakage Syndrome)

## 4.0 STUDY ASSESSMENTS

### 4.1 Pre-Treatment Period

During the Pre-Treatment Period, subjects are consented and qualified (screened) for the study. Informed consent must be obtained before initiation of any clinical screening procedure that is performed solely for the purpose of determining eligibility for this study. Evaluations performed as part of routine care before informed consent can be considered as screening evaluations if done within the defined screening period, and if permitted by the site's institutional review board (IRB)/ ethics committee (EC) policies. Informed consent may be obtained within 42 days prior to first dose of study treatment. At informed consent, subjects will be assigned a subject identifier at time of registration.

For each subject, the Pre-Treatment Period ends upon receipt of the first dose of study treatment or final determination that the subject is ineligible for the study.

### 4.2 Study Treatment Period

Pregnancy Test: In Women of child Bearing Potential (WOCBP) prior to dosing nivolumab. A serum or urine pregnancy testing is required within 7 days of study enrollment, then every 6 weeks. [more frequently if required by local standard]. After discontinuation from nivolumab these should be repeated at approximately 30 days and approximately 70 days [or more frequently if required by local standard].

Laboratory testing prior to each dose: Within 72 hrs prior to re-dosing to include CBC w/ differential, LFTs (ALT, AST, total bilirubin, alkaline phosphatase), BUN or serum urea level, creatinine, Ca, Na, K, Cl, Glucose, TSH (with Free T4 and Free T3). Thyroid function testing should be done at weeks 7 and 13, and then 6 and 12 months post

enrollment. If the subject is unable to have a study assessment taken within the defined time window due to an event outside of his or her control (e.g., clinic closure, personal emergency, inclement weather, vacation), the assessment should be performed as close as possible to the required schedule.

Subjects should be instructed to inform the investigator of any AEs. Subjects experiencing dizziness, sleepiness, or other symptoms that could influence alertness or coordination should be advised not to drive or operate other heavy machinery.

Subjects may receive study treatment until the earlier of PD or unacceptable toxicity. Regular tumor assessments including cystoscopies and biopsies should be performed according to the protocol guidelines if patient discontinues study therapy due to toxicities and if feasible per their medical status.

The Treatment Period ends when a subject receives his or her last dose of study treatment; the subject then enters the Post-Treatment Period.

### 4.3 Post-Treatment Period

Subjects will be followed per protocol guidelines. If patients have residual or progressive disease noted during evaluation in the first 12 months, requiring other therapeutic modalities, then they will enter follow up phase. Additional follow-up will occur for subjects with AEs related to study treatment that are ongoing at every visit, and for subjects with SAEs related to study treatment that occur after the time of this visit.

### 4.4 Laboratory Assessments

Local laboratories will perform all laboratory tests. Blood samples for standard hematology and serum chemistry will be done using standard procedures. Surveillance cystoscopies and biopsies as indicated are recommended every 3 months during the first 12 months after starting study therapy.

A cystoscopy and biopsy should be performed at any time prior to study entry, 13 weeks, 6 months, and 12 months after start of study treatment. At 9 months cystoscopy needs to be done and biopsies are done if clinically indicated and send archival slides if available. These assessments are considered standard of care and maybe delayed +/-28 days per

insurance requirements. Archival slides from pre-therapy biopsy and from week 13, 6 months, and 12 months need to be sent to:

Julie Boerner, Ph.D.
Karmanos Cancer Institute
4100 John R, Detroit MI 48201
Correlative Sciences Lab Rm 808
Tel # 313-576-8351
E-mail: boernerj@karmanos.org

Karri Stark, M.S.
Karmanos Cancer Institute
4100 John R, Detroit MI 48201
Correlative Sciences Lab Rm 808
Tel # 313-576-8248
Email: starkka@karmanos.org

## 4.5 Tumor Assessment

**Response criteria:**

For measurable disease in the bladder and/or lymph node/s, RECIST criteria 1.1 will be used [14].

**THE RECIST 1.1 CRITERIA WITH UNIDIMENSIONAL MEASUREMENT ARE TO BE USED FOR MEASURABLE DISEASE RESPONSE EVALUATION**

**Methods of Assessment**

The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during follow-up. CT is the best currently available and reproducible method to measure lesions selected for response assessment. MRI is also acceptable in certain situations (e.g., for body scans but not for lung). Lesions on a chest X-ray may be considered measurable lesions if they are clearly defined and surrounded by aerated lung. However, CT is preferable.

**Baseline Disease Assessment**

All baseline evaluations should be performed as closely as possible to the beginning of treatment and never more than 42 days before the beginning of the treatment.

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

- 10 mm by CT scan (CT scan slice thickness no greater than 5 mm; when CT scans have slice thickness >5 mm, the minimum size should be twice the slice thickness).
- 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 is recommended to be no greater than 5 mm). At baseline and in follow-up, only the short axis will be measured and followed.

**Non-measurable lesions**

Non-measurable lesions are all other lesions, including small lesions (longest diameter <10 mm or pathological lymph nodes with 10 to <15 mm short axis), as well as truly non-measurable lesions.

**Target Lesions**

- All measurable lesions up to a maximum of two lesions per organ and five lesions in total, representative of all involved organs, should be identified as target lesions and recorded and measured at baseline.
- Target lesions should be selected on the basis of their size (lesions with the longest diameter) and be representative of all involved organs, as well as their suitability for reproducible repeated measurements.
- All measurements should be recorded in metric notation using calipers if clinically assessed. A sum of the diameters (longest for non-nodal lesions, short axis for nodal lesions) for all target lesions.

**Non-target Lesions**

All lesions (or sites of disease) not identified as target lesions, including pathological lymph nodes and all non-measurable lesions, should be identified as non-target lesions and be recorded at baseline. Measurements of these lesions are not required and they should be followed as 'present', 'absent' or in rare cases, 'unequivocal progression'.

**Evaluation 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 diameters of target lesions, taking as reference the baseline sum of diameters.

Progressive Disease (PD):

At least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum on study (this may include the baseline sum). The sum must also demonstrate an absolute increase of at least 5 mm.

Stable Disease (SD):

Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD.

### 4.6 Response Evaluable Patients

All patients registered on the protocol and completing a minimum of one dose of nivolumab therapy followed by clinical or radiologic assessment of disease status.

### 4.7 Toxicity- Evaluable patients

All patients registered on the protocol and starting therapy with nivolumab will be considered toxicity evaluable.

### 4.8 Metastasis-Free Survival (MFS)

The time from start of therapy to the appearance of metastases or cancer related death.

### 4.9 Progression-Free Survival (PFS)

PFS will be measured from treatment start date to date of first documented disease relapse/progression, or death from urothelial cancer whichever occurs first. If patients have residual invasive disease noted at cystoscopy and biopsy post therapy they are deemed to have disease progression at the time of the procedure. After treatment is discontinued/completed, patients will be followed every 3 months for progression and survival for a maximum of 5 years.

### 4.10 Overall Survival (OS)

OS will be measured from treatment start date to death or last follow up. After treatment is discontinued for any reason, patients will be followed every 3 months for progression and survival for a maximum of 5 years.

## 5.0 ADVERSE EVENT REPORTING

### 5.1 Adverse Events and Laboratory Abnormalities

Toxicity will be graded per CTCAE version 4.03. An AE is any untoward medical occurrence in a patient or clinical investigation subject who has been enrolled in a clinical study and who may have been given an investigational product, regardless of whether or not the event is assessed as related to the study treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of an investigational product, regardless of whether or not the event is assessed as related to the investigational product. Pre-existing medical conditions that worsen during a study should be recorded as AEs. Abnormal laboratory values, electrocardiogram (ECG) findings, or vital signs are to be recorded as AEs if they require clinical intervention or results in changes in study therapy. All untoward events that are thought to be probably/definitely treatment related should be followed until resolution even after study treatment has been discontinued. This requirement includes AEs from unscheduled as well as scheduled visits.

As soon as an investigator becomes aware of an AE that meets the definition of 'serious,' this should be documented to the extent that information is available.

- This report must be submitted by the study site to Karmanos Cancer Institute and Bristol-Myers Squibb within 24 hours via a Medwatch form, even if it is not felt to be drug related.
- Email: vaishamn@karmanos.org or dickowb@karmanos.org
- The investigator agrees to provide supplementary information requested by the PI or designee.

- Pregnancy, although not itself an SAE, should also be reported on a Medwatch form and be followed up to determine outcome, including spontaneous or voluntary termination, details of birth, and the presence or absence of any birth defects or congenital abnormalities.

## 5.2 Local IRB reporting

Reporting is also required per the local IRB reporting procedures for each site.

## 5.3 Adverse event reporting to BMS

- All treatment related or unrelated Serious Adverse Events (SAEs) that occur following the subject's written consent to participate in the study through 100 days of discontinuation of dosing must be reported to Karmanos Cancer Institute and BMS Worldwide Safety.
- For subjects consented and never treated with study drug, SAEs should be collected for 30 days from the date of consent.
- If the BMS safety address is not included in the protocol document (e.g. multicenter studies where events are reported centrally), the procedure for safety reporting must be reviewed/approved by the BMS Protocol Manager. Procedures for such reporting must be reviewed and approved by BMS prior to study activation.
- The Medwatch/BMS form should be used to report SAEs. If the BMS form cannot be used, another acceptable form (i.e. CIOMS or Medwatch) must be reviewed and approved by BMS. The BMS protocol ID number must be included on whatever form is submitted by the Sponsor/Investigator.
- Following the subject's written consent to participate in the study, all SAEs, whether related or not related to study drug, are collected, including those thought to be associated with protocol-specified procedures. The investigator should report any SAE occurring after these time periods that is believed to be related to study drug or protocol-specified procedure. For drugs with potential for delayed SAEs (e.g., delayed excretion of the parent or active metabolites), a longer follow-up period may be warranted to allow collection of these SAEs, laboratory tests, and other assessments.
- For studies with long-term follow-up periods in which safety data are being reported, include the timing of SAE collection
- In accordance with local regulations, BMS will notify investigators of all reported SAEs that are suspected (related to the investigational product) and unexpected (i.e., not previously described in the IB). In the European Union (EU), an event meeting these criteria is termed a Suspected, Unexpected Serious Adverse Reaction (SUSAR). Investigator notification of these events will be in the form of an expedited safety report (ESR).

- Other important findings which may be reported by the as an ESR include: increased frequency of a clinically significant expected SAE, an SAE considered associated with study procedures that could modify the conduct of the study, lack of efficacy that poses significant hazard to study subjects, clinically significant safety finding from a nonclinical (eg, animal) study, important safety recommendations from a study data monitoring committee, or sponsor decision to end or temporarily halt a clinical study for safety reasons.
- Upon receiving an ESR from BMS, the investigator must review and retain the ESR with the IB. Where required by local regulations or when there is a central IRB/IEC for the study, the sponsor will submit the ESR to the appropriate IRB/IEC. The investigator and IRB/IEC will determine if the informed consent requires revision. The investigator should also comply with the IRB/IEC procedures for reporting any other safety information.
- In addition, suspected serious adverse reactions (whether expected or unexpected) shall be reported by BMS to the relevant competent health authorities in all concerned countries according to local regulations (either as expedited and/or in aggregate reports).

## 5.4 Serious Adverse Event Collection and Reporting

Following the subject's written consent to participate in the study, all SAEs, whether related or not related to study drug, must be collected, including those thought to be associated with protocol-specified procedures. All SAEs must be collected that occur within 100 days of discontinuation of dosing.

All SAEs must be collected that occur during the screening period. If applicable, SAEs must be collected that relate to any protocol-specified procedure (e.g., a follow-up skin biopsy). The investigator should report any SAE that occurs after these time periods that is believed to be related to study drug or protocol-specified procedure.

SAEs, whether related or not related to study drug, and pregnancies must be reported to Karmanos Cancer Institute and BMS within 24 hours. SAEs must be recorded on Medwatch form; pregnancies also on a Medwatch form.

**SAE Email Address:** Worldwide.Safety@BMS.com

**SAE Facsimile Number:** 609-818-3804

If only limited information is initially available, follow-up reports are required. (Note: Follow-up SAE reports should include the same investigator term(s) initially reported.)

If an ongoing SAE changes in its intensity or relationship to study drug or if new information becomes available, a follow-up SAE report should be sent within 24 hours to the BMS (or designee) using the same procedure used for transmitting the initial SAE report.

All SAEs should be followed to resolution or stabilization.

The Sponsor/Investigator will ensure that all SAEs in the clinical database are reported to BMS and any applicable health authority during the conduct of the study including periodic reconciliation.

**For studies conducted under an Investigator IND in the US include the following timelines or text:**

For studies conducted under an Investigator IND in the US, any event that is both serious unexpected and related must be reported to the Food and Drug Administration (FDA) as soon as possible and no later than 7 days (for a death or life-threatening event) or 15 days (for all other SAEs) after the investigator's or institution's initial receipt of the information. BMS will be provided with a simultaneous copy of all adverse events filed with the FDA.

SAEs should be reported on MedWatch Form 3500A, which can be accessed at: http://www.accessdata.fda.gov/scripts/medwatch/.

MedWatch SAE forms should be sent to the FDA at:
MEDWATCH
5600 Fishers Lane
Rockville, MD 20852-9787
Fax: 1-800-FDA-0178 (1-800-332-0178)
http://www.accessdata.fda.gov/scripts/medwatch/

All SAEs should simultaneously be faxed or e-mailed to BMS at:

Global Pharmacovigilance & Epidemiology
Bristol-Myers Squibb Company
Fax Number: 609-818-3804
Email: Worldwide.safety@bms.com

- An SAE report should be completed for any event where doubt exists regarding its seriousness.
- For studies with long-term follow-up periods in which safety data are being reported, include the timing of SAE collection in the protocol.
- If the investigator believes that an SAE is not related to study drug, but is potentially related to the conditions of the study (such as withdrawal of previous therapy or a complication of a study procedure), the relationship should be specified in the narrative section of the SAE Report Form.
- If only limited information is initially available, follow-up reports are required. (Note: Follow-up SAE reports should include the same investigator term(s) initially reported.)
- If an ongoing SAE changes in its intensity or relationship to study drug or if new information becomes available, a follow-up SAE report should be sent within 24 hours to BMS using the same procedure used for transmitting the initial SAE report.

All SAEs should be followed to resolution or stabilization. All SAEs should be followed to resolution or stabilization.

## 5.5 Definitions

**SERIOUS ADVERSE EVENTS**

A ***Serious Adverse Event (SAE)*** is any untoward medical occurrence that at any dose:

- results in death
- 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 or causes prolongation of existing hospitalization (see **NOTE** below)
- results in persistent or significant disability/incapacity
- is a congenital anomaly/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 that do not result in hospitalization.)
- Potential drug induced liver injury (DILI) is also considered an important medical event.
- Suspected transmission of an infectious agent (e.g., pathogenic or nonpathogenic) via the study drug is an SAE.
- Although pregnancy, overdose, and cancer are not always serious by regulatory definition, these events must be handled as SAEs.

The following hospitalizations are not considered SAEs in this clinical trial::

- a visit to the emergency room or other hospital department < 24 hours, that does not result in admission (unless considered an important medical or life-threatening event)
- elective surgery, planned prior to signing consent
- admissions as per protocol for a planned medical/surgical procedure
- routine health assessment requiring admission for baseline/trending of health status (e.g., routine colonoscopy)
- Medical/surgical admission other than to remedy ill health and planned prior to entry into the study. Appropriate documentation is required in these cases

- Admission encountered for another life circumstance that carries no bearing on health status and requires no medical/surgical intervention (eg, lack of housing, economic inadequacy, caregiver respite, family circumstances, administrative reason).

Potential Drug Induced Liver Injury (DILI)

Wherever possible, timely confirmation of initial liver-related laboratory abnormalities should occur prior to the reporting of a potential DILI event. All occurrences of potential DILIs, meeting the defined criteria, must be reported as SAEs

Potential drug induced liver injury is defined as:

1) ALT or AST elevation > 3 times upper limit of normal (ULN)
   AND
2) Total bilirubin > 2 times ULN, without initial findings of cholestasis (elevated serum alkaline phosphatase)
   AND
3) No other immediately apparent possible causes of AST/ALT elevation and hyperbilirubinemia, including, but not limited to, viral hepatitis, pre-existing chronic or acute liver disease, or the administration of other drug(s) known to be hepatotoxic.

**ADVERSE EVENTS**

An Adverse Event (AE) is defined as any new untoward medical occurrence or worsening of a preexisting medical condition in a clinical investigation subject administered an investigational (medicinal) product and that does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (such as an abnormal laboratory finding), symptom, or disease temporally associated with the use of investigational product, whether or not considered related to the investigational product.

The causal relationship to study drug is determined by a physician and should be used to assess all adverse events (AE). The casual relationship can be one of the following:

Related: There is a reasonable causal relationship between study drug administration and the AE.

Not related: There is not a reasonable causal relationship between study drug administration and the AE.

The term "reasonable causal relationship" means there is evidence to suggest a causal relationship.

Adverse events can be spontaneously reported or elicited during open-ended questioning, examination, or evaluation of a subject. (In order to prevent reporting bias, subjects should not be questioned regarding the specific occurrence of one or more AEs.)

**NONSERIOUS ADVERSE EVENT**

- Nonserious Adverse Events are to be provided to BMS in aggregate via interim or final study reports as specified in the agreement or, if a regulatory requirement [e.g. IND US trial] as part of an annual reporting requirement.
- Nonserious AE information should also be collected from the start of a placebo lead-in period or other observational period intended to establish a baseline status for the subjects.

A ***nonserious adverse event*** is an AE not classified as serious.

**Nonserious Adverse Event Collection and Reporting**

The collection of nonserious AE information should begin at initiation of study drug. All nonserious adverse events (not only those deemed to be treatment-related) should be collected continuously during the treatment period and for a minimum of 100 days following the last dose of study treatment.

Nonserious AEs should be followed to resolution or stabilization, or reported as SAEs if they become serious. Follow-up is also required for nonserious AEs that cause interruption or discontinuation of study drug and for those present at the end of study treatment as appropriate.

**Laboratory Test Abnormalities**

All laboratory test results captured as part of the study should be recorded following institutional procedures. Test results that constitute SAEs should be documented and reported as such.

The following laboratory abnormalities should be documented and reported appropriately:

any laboratory test result that is clinically significant or meets the definition of an SAE

any laboratory abnormality that required the subject to have study drug discontinued or interrupted

any laboratory abnormality that required the subject to receive specific corrective therapy.

**Pregnancy**

If, following initiation of the investigational product, it is subsequently discovered that a study subject is pregnant or may have been pregnant at the time of investigational product exposure, including during at least 6 halflives after product administration, the investigational product will be permanently discontinued in an appropriate manner (eg, dose tapering if necessary for subject safety).

The investigator must immediately notify Worldwide Safety @BMS of this event via the Pregnancy Surveillance Form in accordance with SAE reporting procedures.

Follow-up information regarding the course of the pregnancy, including perinatal and neonatal outcome and, where applicable, offspring information must be reported on the Pregnancy Surveillance Form [provided upon request from BMS]

Any pregnancy that occurs in a female partner of a male study participant should be reported to BMS. Information on this pregnancy will be collected on the Pregnancy Surveillance Form.

**Overdose**

An overdose is defined as the accidental or intentional administration of any dose of a product that is considered both excessive and medically important. All occurrences of overdose must be reported as an SAE.

**Other Safety Considerations**

Any significant worsening noted during interim or final physical examinations, electrocardiograms, x-rays, and any other potential safety assessments, whether or not these procedures are required by the protocol, should also be recorded as a nonserious or serious AE, as appropriate, and reported accordingly.

## 6.0 CORRELATIVE STUDIES (APPENDIX G)

### 6.1 Tumor Biopsy Samples

- Tumor biopsy samples will be collected pre-therapy, at week 13, 6 months, 9 months (if clinically indicated),12 months and at time of progression. 10 unstained slides or tumor block is required.

**Contact information for tissue pickup andshipping:**

Julie Boerner, Ph.D.
Karmanos Cancer Institute
4100 John R, Detroit MI 48201
Correlative Sciences Lab Rm 808
Tel # 313-576-8351
E-mail: boernerj@karmanos.org

Karri Stark, M.S.
Karmanos Cancer Institute
4100 John R, Detroit MI 48201
Correlative Sciences Lab Rm 808
Tel # 313-576-8248
Email: starkka@karmanos.org

Please send email with requisition form at time of submission to

boernerj@karmanos.org

and

dickowb@karmanos.org

## 6.2 Tumor Tissue Specimens (Appendix G)

Tumor tissue specimens in the form of a paraffin embedded block or a minimum of 10 unstained slides, with a single section on positively charged slides will be submitted for PD-1 and PD-L1 immunohistochemistry (IHC) assessment. These biopsy samples should be excisional, incisional, punch or core needle. Fine needle aspirates or other cytology specimens are insufficient for downstream biomarker analyses. PD-1 and PD-L1 stained tissue sections will be assessed by a pathologist and scored as positive on a 1+ to 3+ scale if membrane staining is observed.

These tumor samples, may also be assessed for the expression of other immune or related genes, RNAs and/or proteins, as well as, the presence of immune cell populations using a variety of methodologies inclusive of, but not limited to immunohistochemistry (IHC), qRT-PCR, genetic mutation detection and fluorescent in-situ hybridization (FISH). Various molecular markers with potential predictive value are currently under investigation and may be assessed in this study. These tumor tissue biomarkers include, but are not limited to PD-1, PD-L2, tumor infiltrating lymphocytes (TILs) or subpopulations of TILs and a Th1 immune mRNA expression signature. In addition, other methods of measuring tumor PD-L1 expression may also be assessed. Mutation load will be explored on tumor tissue. Tissue may be assessed for residual tumor cells and for markers expected to accompany tumor shrinkage in this study, including, but not limited to TILs and subsets thereof.

## 6.3 Immune response monitoring [Appendix G]

Peripheral blood (30 ml) will be drawn pre-treatment, and at following time-points (week 7 and 13, 6 months, and 12 months) after initiation of immunotherapy. The plasma and PBMC will be isolated following a standard protocol (SOP attached). In order to maintain consistent quality, all clinical sites will isolate plasma and PBMC following the exact same protocol and cryo-ship the samples to KCI for further analysis. See appendix G for details regarding sample collection and shipping. The samples should be sent to Dr. Parajuli, contact information given below.

**Prahlad Parajuli, Ph.D.**
Elliman Clinical Research Building, #2029
421 E. Canfield St.,
Detroit, MI 48201.
Cell 2485067180 (preferred)
Ph: 313-578-4268 (Off); 313-577-0629 (Lab)
Email: pparajuli@med.wayne.edu

The correlative studies will focus on any phenotypic or functional changes with regards to the T cell help, cytotoxicity or regulatory characteristics as well as B cell antibody profile following immunotherapy compared to the pre-treatment samples. The plasma will be analyzed for levels of twenty-five different cytokines, chemokines and growth factors including, IFN-γ, TNF-α, MCP-1, GM-CSF, IL-1, IL-2, IL-6, IL-8 and IL-10, using a multiplex cytokine array. A multi-parametric flow cytometry will be performed for phenotypic characterization of immune cell subsets, intracellular cytokine staining in specific subsets as well as to analyze cytotoxic T cell activation. Tumor antigen-specific immune cell functional profiling will be performed via ELISPOT analysis of stimulated and non-stimulated T and B cells. While T cells will be analyzed for IFN-γ and Granzyme B secretion, B cells will be assayed for antigen-specific IgG and IgM production.

## 6.4 Quality of Life (QOL) Questionnaires [Appendix F]

The QOL questionnaire will be administered at the 15 time points listed in the header of the Study Calendar in Section 2.3. The FACIT symptom index score for cancer and specific bladder symptom index questionnaires will be completed at a maximum of 15 timepoints starting with pre-therapy, the days of nivolumab therapy, and then 6 and 12 month timepoints The change in score indices will be analyzed by repeated measures analysis and modeling and will be reported.

## 7.0 TREATMENT PLAN, MODIFICATIONS AND CONCOMITANT THERAPY

### 7.1 Product Information Table

Please also see Drug Information Appendix C

The study medication (Nivolumab) will be shipped to each site by BMS.

**Product Description: Nivolumab (Other names = MDX-1106, ONO-4538, anti-PD-1)**

| Product Description and Dosage Form | Potency | Primary Packaging (Volume)/ Label Type | Secondary Packaging (Qty) /Label Type | Appearance | Storage Conditions (per label) |
|---|---|---|---|---|---|
| Nivolumab (BMS-936558-01)* Injection drug product is a sterile, non-pyrogenic, single-use, isotonic aqueous solution formulated at 10 mg/mL | 100 mg/Vial (10 mg/mL). | Carton of 5 or 10 vials | 10-cc Type 1 flint glass vials stoppered with butyl stoppers and sealed with aluminum seals. | Clear to opalescent, colorless to pale yellow liquid. May contain particles | **BMS-936558-01 Injection** must be stored at 2 to 8 degrees C (36 to 46 degrees F) and protected from light and freezing |

*Nivolumab may be labeled as BMS-936558-01 Solution for Injection

If stored in a glass front refrigerator, vials should be stored in the carton. Recommended safety measures for preparation and handling of nivolumab include laboratory coats and gloves.

For additional details on prepared drug storage and use time of nivolumab under room temperature/light and refrigeration, please refer to the BMS-936558 (nivolumab) Investigator Brochure section for "Recommended Storage and Use Conditions"

### 7.2 Handling and Dispensing

The investigator should ensure that the study drug is stored in accordance with the environmental conditions (temperature, light, and humidity) as per product information and the Investigator Brochure and per local regulations. It is the responsibility of the investigator to ensure that investigational product is only dispensed to study subjects. The

investigational product must be dispensed only from official study sites by authorized personnel according to local regulations. If concerns regarding the quality or appearance of the study drug arise, the study drug should not be dispensed and contact BMS immediately.

Please refer to the current version of the Investigator Brochure and/or shipment reference sheets for additional information on storage, handling, dispensing, and infusion information for nivolumab.

**Destruction**

Sponsor/Investigator drug destruction is allowed provided the following minimal standards are met:

- On-site disposal practices must not expose humans to risks from the drug.
    - On-site disposal practices and procedures are in agreement with applicable laws and regulations, including any special requirements for controlled or hazardous substances.
- Written procedures for on-site disposal are available and followed. The procedures must be filed with the Sponsor SOPs and a copy provided to BMS upon request.
- Records are maintained that allow for traceability of each container, including the date disposed of, quantity disposed, and identification of the person disposing the containers. The method of disposal, ie, incinerator, licensed sanitary landfill, or licensed waste disposal vendor must be documented.
- Accountability and disposal records are complete, up-to-date, and available for BMS to review throughout the clinical trial period as per the study agreement.
- If conditions for destruction cannot be met, please contact BMS.
- It is the Sponsor Investigator's responsibility to arrange for disposal of all empty containers, provided that procedures for proper disposal have been established according to applicable federal, state, local, and institutional guidelines and procedures, and provided that appropriate records of disposal are kept.

### 7.3 Dose calculations and administration

Nivolumab will be given every two weeks at a dose of 240 mg to be administered as an approximately 30-60 minute +/- 10 min IV infusion.

Nivolumab Injection, 100 mg (10 mg/mL) Nivolumab injection is to be administered as an IV infusion through a 0.2-micron to 1.2-micron pore size, low-protein binding polyethersulfone membrane in-line filter at the protocol-specified doses. 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 .35 mg/mL. Care must be taken to assure sterility of the prepared solution as the product does not contain any antimicrobial preservative or bacteriostatic agent.

Subjects may be dosed no less than 12 days from the previous dose of drug. There are no premedications recommended for nivolumab.

Subjects should be carefully monitored for infusion reactions during nivolumab administration. If an acute infusion reaction is noted, subjects should be managed according to Appendix C.

Doses of nivolumab may be interrupted, delayed, or discontinued depending on how well the subject tolerates the treatment.

## 7.4 Dose Modifications

Dose reductions or dose escalations are not permitted.

## 7.5 Dose Delay Criteria

Because of the potential for clinically meaningful 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 Dfor citation examples]

Dose delay criteria apply for all therapy related adverse events (regardless of whether or not the event is attributed to nivolumab).

**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 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 investigator, warrants delaying the dose of study medication.

Subjects who require delay of nivolumab should be re-evaluated as clinically indicated and resume nivolumab dosing when re-treatment criteria are met.

## 7.6 Criteria to Resume Treatment

Subjects may resume treatment with study drug 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. *Subjects with persistent Grade 1 pneumonitis after completion of a steroid taper over at least 1 month may be eligible for retreatment if investigator allows, but should be discussed with the PI.*
- Drug-related endocrinopathies adequately controlled with only physiologic hormone replacement may resume treatment *if investigator allows, but should be stated in the protocol clearly*.

If the criteria to resume treatment are met, the subject should restart treatment at the next scheduled timepoint per protocol.

If treatment is delayed or interrupted for > 6 weeks, the subject must be permanently discontinued from study therapy, except as specified in discontinuation section.

## 7.7 Management Algorithms

| |
|---|
| Guidelines for the management of immune related events can be found in the current Investigator Brochure AND in the approved USPI in the US. 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 G] of this protocol. The guidance provided in these algorithms should not replace the Investigator's medical judgment but should complement it.

## 7.8 Discontinuation Criteria

Treatment should be permanently discontinued for the following:

- Grade 4 neutropenia lasting > 7 days
- 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 > 8 x ULN
            - Total bilirubin > 5 x ULN
            - Concurrent AST or ALT > 3 x ULN and total bilirubin > 2 x ULN

- AST or ALT > 3 x ULN with the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia (>5%) should lead to treatment discontinuation.
- 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 leucopenia
    - 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 Investigator [as allowed by protocol]
- Any dosing interruption lasting > 6 weeks with the following exceptions:
    - 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 Investigator. 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
- Any adverse event, laboratory abnormality, or intercurrent illness which, in the judgment of the Investigator, presents a substantial clinical risk to the subject with continued nivolumab dosing

### 7.9 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 4.0 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 [eg, 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 [ie, not rapidly responsive to symptomatic medication and/or brief interruption of infusion]; recurrence of symptoms following initial improvement; hospitalization indicated for other clinical sequelae [eg, 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 (eg, appearance of a localized or generalized pruritis within 1 week after treatment), symptomatic treatment may be given (eg, oral antihistamine, or corticosteroids).

### 7.10 Concomitant Therapy

**Permitted Therapy**

Subjects are permitted to use topical, ocular, intra-articular, intranasal, and inhalational corticosteroids (with minimal systemic absorption). Physiologic replacement doses of systemic corticosteroids are permitted, even if > 10 mg/day prednisone equivalents. A brief course of corticosteroids for prophylaxis (eg, contrast dye allergy) or for treatment of non-autoimmune conditions (eg, delayed-type hypersensitivity reaction caused by contact allergen) is permitted.

## 8.0 STATISTICAL CONSIDERATIONS

### 8.1 Objectives

Primary Objective:

To compare the 12-month rate of progression-free survival (PFS) achieved with the combination of nivolumab, a programmed death (PD-1) inhibitor, and radiation therapy in localized/locally advanced urothelial cancer patients, who are ineligible for chemotherapy, to a historical control reference 12-month PFS rate.

Secondary Objectives:

1) To assess the toxicity of concurrent nivolumab and radiation therapy in urothelial cancer.
2) To determine overall response rate (ORR).
3) To determine metastasis-free survival (MFS).
4) To determine overall survival (OS).
5) To evaluate the quality of life (QOL) and bladder functioning during and after

the therapy.

6) To explore the relationships of PD-1 expression, PDL-1 expression, and the Th1/Th2 cytokine ratio to clinical outcomes (response, PFS, MFS, and OS).

## 8.2 Endpoints

8.2.1 The primary endpoint (PFS) is defined in Section 4.9.

8.2.2 The secondary endpoints are defined in the following protocol sections:

Toxicity assessment is defined in Section 5, and toxicity-evaluable patients are defined in Section 4.7.

Response is defined in Section 4.5, and response-evaluable patients are defined in Section 4.6.

MFS and OS are defined in Sections 4.8 and 4.10, respectively.

QoL and bladder functioning questionnaires (FACT-BI and BISI) are specified in Section 7.3 and shown in Appendix E.

PDL-1 (and other biomarkers) are listed in Section 7.2, and will be assessed by IHC (or other assay methods).

## 8.3 Design

This is a 1-arm 1-stage survival type design focused on the primary endpoint of the 12-month PFS rate. The study design assumptions are:

1) A population reference value of 50% 12-month PFS rate from standard of care with RT alone (from Supplementary Appendix Figure 1(a) in reference [4] );
2) A hypothesized 75% 12-month PFS rate for patients treated with Nivolumab+RT;
3) Exponentially distributed PFS times;
4) Accrual time of 24 months;
5) An additional follow-up time of 12 months for all patients;
6) Significance level alpha = 0.025 (1-sided, due to the directional hypothesis);
7) Power = 0.95 (high due to the unmet need for improved therapy options for study eligible patients).

Under these 7 assumptions, the study will require N=30 evaluable patients, as calculated using the "One Arm Survival" program on the www.crab.org website. Evaluable for

PFS and toxicity evaluable (see Section 4.7) have the same definition: registered and having started Nivolumab therapy. Allowing for up to 10% of enrolled patients who may become inevaluable, up to 34 patients may need to be enrolled.

## 8.4 Analysis

8.4.1 For the Primary Objective, the censored PFS distribution will be summarized with the Kaplan-Meier (K-M) survivorship estimate. A graph of the K-M curve for PFS will be generated along with the Hall-Wellner 95% confidence band, and a display of the number of patients at risk at several time points, below the X-axis. Summary statistics (12-month PFS rate, median PFS, etc.) will be calculated from the K-M life table, each one with its respective 95% confidence interval (CI). To test whether the point estimate of the 12-month PFS rate is statistically significantly greater than the assumed historical reference value of 0.50, the point estimate will be compared to the upper critical value of 0.64 obtained from the "One Arm Survival" program mentioned in Section 8.3.

8.4.2 For Secondary Objective (1) toxicity rates will be estimated among the toxicity evaluable patients (defined in Section 4.7). Frequency distributions of each toxicity type by severity grade will be generated. For a given grade(s), the point estimate of the toxicity rate will be computed, along with its 95% (Wilson type) CI.

8.4.3 For Secondary Objective (2), the ORR will be estimated among the response evaluable patients (defined in Section 4.6), and among all patients. Frequency distributions of best response will be generated for each of those sets of patients. The point estimate of the ORR will be computed, along with its 95% (Wilson type) CI.

8.4.4 For Secondary Objectives (3) and (4), summary statistics of MFS and OS will be calculated from their respective K-M life tables in the similar fashion as described in Section 8.4.1 for OS. K-M graphs of the censored MFS and OS distributions will also be generated.

8.4.5 For Secondary Objective (5), the QOL data will be used to test the following hypotheses:

1. Demographics and clinical variables (age, sex, race/ethnicity) will be related to length of time on trial (i.e., days or weeks);
2. Demographic and clinical variables (cancer stage, performance status, number of comorbidities) will be related to: (a) average levels of QOL; and (b) variability in QOL over the course of the trial.

We will use a linear mixed-effects model to test the association between baseline patient factors (demographic and clinical measures) and QOL. The model will have a random intercept, slope, and leading coefficient for the measurement of QOL across all 15 time points identified in the Study Calendar, Section 2.3. The patient factors will be used as predictors of QOL with baseline QOL as a covariate. The association will be investigated based on the statistical testing for each of the slope and intercept fixed-effects using a Wald test. As the measurements on each individual would be correlated, the first-order autoregressive AR(1) residual will be used for the residual variance-covariance structure. We will also investigate other variance-covariance residual structures to further improve the model fitting. The final model will be selected based on the Akaike information criterion (AIC).

8.4.6 For Secondary Objective (6), the tissue markers (e.g., PD-1, PDL-1, TILs) and serum marker Th1/Th2 cytokine ratio first will be summarized descriptively. The categorical markers PD-1 and PDL-1 will be summarized via frequency distributions (over their IHC expression categories of 0, 1+, 2+, and 3+). The continuous markers (e.g., TILs, Th1/Th2 cytokine ratio, etc.) will be summarized with standard descriptive statistics. These descriptive analyses of the tissue and plasma biomarkers will be performed for each time point at which the each marker is determined.

Response (CR/PR vs not) will be modeled as a function of a dichotomized version of prestudy PD-1 and PDL-1 expression (separately) using exact logistic regression. Similar logistic model analyses of those tissue markers determined at other time points prior to response determination will also be performed. Similar modeling will be performed for the continuous (ungrouped) markers (e.g., TILs from tissue, and the Th1/Th2 cytokine ratio ). The statistical goal of these exploratory analyses is to obtain the point and 95% CI

estimates of the odds ratio (OR), and to simply determine the direction and approximate magnitude of these associations for use in planning a subsequent study.

Censored PFS will be modeled as a function of a dichotomized version of prestudy PD-1 and PDL-1 expression (separately) using Cox proportional hazards (PH) regression. Time-dependent Cox model analyses of those tissue markers determined at all time points will also be performed. A similar Cox modeling strategy will be used for the continuous (ungrouped) markers (e.g., TILs from tissue, and the_Th1/Th2 cytokine ratio from serum). For all Cox models, the PH assumption will be examined graphically by inspection of log(-log) survival plots, and of Epanechnikov kernel-smoothed hazard functions. Non-PH for a given marker variable will be incorporated into the Cox model by including a ( ln(PFS) * marker ) interaction term in the Cox model. The statistical goal of these exploratory analyses is to obtain the point and 95% CI estimates of the hazard ratio (HR), and to simply determine the direction and approximate magnitude of these associations for use in planning a subsequent study.

### 8.5 Expected accrual rate, accrual duration, and total study duration

The expected accrual rate is 3-4 patients/year/institution. It is expected that 2-3institutions will participate in this study, yielding a combined expected accrual rate of 12 –15patients/year. At that rate, 34 patients (to yield 30 evaluable for PFS) would be accrued in – 30 - 36 months, a time interval which contains the 24-month assumed accrual duration in the study design.

Allowing for the required 12 months of additional follow-up time, the primary endpoint should be obtained for all patients in – 32 - 46 months (i.e., 2.7 – 3.8 years).

Allowing for 4 more months to determine all correlatives on the last few patients enrolled, that would take 36 – 50 months (i.e., 3.0 – 4.2 years).

Finally, since follow-up for PFS and OS will occur for a maximum of 5 years (as per Sections 2.3, 4.9 and 4.10), then the total study duration is a maximum of 60 months (i.e., 5.0 years).

## 9.0 ETHICAL ASPECTS

### 9.1 Local Regulations

The study must fully adhere to the principles outlined in "Guideline for Good Clinical Practice" (GCP) ICH E6 Tripartite Guideline (January 1997). The investigator/s will ensure that the conduct of the study complies with the basic principles of GCP as outlined in the current version of 21 Code of Federal Regulations, subpart D, Part 312, "Responsibilities of Sponsors and Investigators" Part 50, "Protection of Human Subjects" and Part 56, "Institutional Review Boards."

### 9.2 Informed Consent

It is the responsibility of the investigator, or a person designated by the investigator, to obtain written informed consent from each subject participating in this study after adequate explanation of the aims, methods, anticipated benefits, and potential hazards of the study. In the case where the subject is unable to read, an impartial witness should be present during the entire informed consent discussion. After the subject has orally consented to participation in the trial, the witness's signature on the form will attest that the information in the consent form was accurately explained and understood.

Documentation of informed subject consent must be completed appropriately. If new safety information results in significant changes in the risk/ benefit assessment, the consent form should be reviewed and updated as necessary. All subjects (including those who have already completed study therapy) should be informed of the new information, should be given a copy of the revised form, and should give their consent to continue in the study.

### 9.3 Conditions for Modifying the Protocol

Protocol modifications may be made and will be prepared, reviewed, and approved by the principal investigator or representatives of the investigator.

All protocol modifications must be submitted to the IRB/ EC for information and approval in accordance with local requirements and to regulatory agencies if required. Approval must be obtained before any changes can be implemented, except for changes necessary to eliminate an immediate hazard to study subjects or those that involve only logistical or

administrative aspects of the trial (eg, change in data monitor or change of telephone number).

### 9.4 Conditions for Terminating the Study

Karmanos Cancer Institute reserves the right to terminate the study, and investigators reserve the right to terminate their participation in the study, at any time. Should this be necessary, the investigator will arrange the procedures on an individual study basis after review and consultation. In terminating the study, adequate consideration will be given to the protection of the subjects' interests.

## 10.0 STUDY DOCUMENTATION

Accurate and complete study records will be maintained and made available to representatives of the coordinating site as necessary for review and data extraction.

### 10.1 Patient Registration and Data Collection

All patients shall be registered with the Karmanos Cancer Institute Clinical Trials Office at (313) 576-9372 (Brenda Dickow) or Kimberlee Dobson 313-576-9837 or Sarah Rusk 313-576-9771.

At the time of registration, a pre-study form and all information required to verify eligibility shall be necessary on each patient prior to treatment. This form should be faxed to 313-576-8974 and eligibility verification will be sent within 48 hours. Data will be collected and maintained on study specific electronic case report forms in the Oncore Research Enterprise system at Karmanos Cancer Institute. Training and support will be provided for all staff entering data. Data entry must occur within 2 weeks of visits along with submission of applicable source documentation.

### 10.2 Investigator's Files and Required Documents

The investigator must maintain adequate and accurate records to enable the conduct of the study to be fully documented and the study data to be subsequently verified. These documents should be classified into two separate categories as follows: (1) the investigator's study file, and (2) subjects' clinical source documents.

The investigator's study file will contain the protocol and protocol amendments, CRFs, query forms, IRB/ EC and governmental approvals with correspondence, sample informed consent, drug records, staff curriculum vitae and authorization forms, and other appropriate documents and correspondence.

Subjects' clinical source documents include the subjects' hospital/ clinic records; physicians' and nurses' notes; the appointment book; original laboratory, ECG, scans, X-ray, pathology and special assessment reports; signed informed consent forms; consultant letters; and subject screening and enrollment logs.

The investigator must keep these documents on file for at least 2 years after the study has been terminated. After that period, the documents may be destroyed subject to local regulations. If the investigator wants to assign the study records to another party or move them to another location, Karmanos Cancer Institute must be notified in advance.

When source documents are required for the continued care of the subject, appropriate copies should be made for storing outside of the study site.

### 10.3 Source Documents and Background Data

Upon request, the investigator will supply its licensees and collaborators with any required background data from the study documentation or clinic records. This is particularly important when CRFs are illegible or when errors in data transcription are suspected. In case of special problems or governmental queries or requests for audit inspections, it is also necessary to have access to the complete study records, provided that subject confidentiality is protected.

### 10.4 Case Report Forms (CRF)

For enrolled subjects, only data from the procedures and assessments specified in this protocol and required by the CRFs should be submitted on the appropriate CRF. Additional procedures and assessments may be performed as part of the investigator's institution or medical practice standard of care and may not be required for CRF entry.

For each subject enrolled, the CRF (paper or electronic) must be completed and signed by the PI or authorized delegate from the study staff.

All paper forms should be typed or filled out using indelible ink and must be legible. Errors should be crossed out but not obliterated, the correction inserted, and the change initialed and dated by the investigator or his or her authorized delegate.

The investigator should ensure the accuracy, completeness, legibility, and timeliness of the data reported in the CRF and in all required reports. The CRFs will be completed and stored electronically within the Oncore Research Enterprise system at Karmanos Cancer Institute.

### 10.5 Confidentiality of Trial Documents and Subject Records

The investigator must assure that subjects' anonymity will be maintained and that their identities are protected from unauthorized parties. On CRFs or other documents submitted to KCI or designees, subjects should be identified by identification codes and not by their names. The investigator should keep a subject enrollment log showing codes, names, and addresses. The investigator should maintain documents not for submission to KCI or designees (eg, subjects' written consent forms) in strict confidence.

All tumor scans, research samples, photographs, and results from examinations, tests, and procedures may be sent to KCI and its partners or designees for review.

### 10.6 Publication of Data

The Principal Investigator (Protocol Chair) holds the primary responsibility for publication of the study results; provided that the PI will provide any such publication to Bristol Myers Squibb Inc. for review prior to submission and also comply with any provisions regarding publication. The results will be made public within 24 months of the end of data collection. However, if a report is planned to be published in a peer-reviewed journal, then that initial release may be an abstract that meets the requirements of the International Committee of Medical Journal Editors. In any event, a full report of the outcomes should be made public no later than three (3) years after the end of data collection. Authorship for abstracts and manuscripts resulting from this study will be determined according to guidelines established by the International Committee of Medical Journal Editors.

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## 12.0 DATA AND SAFETY MONITORING

Scheduled meetings/ teleconferences will be held monthly or more frequently depending on the activity of the protocol. These meetings will include the protocol investigators and data managers involved with the conduct of the protocol. The Data and Safety Monitoring Committee at the coordinating site (Karmanos Cancer Institute) will have oversight of all patients enrolled on the trial at all participating sites.

During these meetings the investigators will discuss matters related to:

- Safety of protocol participants (Adverse Event reporting)
- Validity and integrity of the data
- Enrollment rate relative to expectation of target accrual, characteristics of participants
- Retention of participants, adherence to the protocol (potential or real protocol violations)
- Data completeness on case report forms and complete source documentation

Completed Data and Safety Monitoring Reports of these regular investigator meetings will be kept on file in the office of the Clinical Trials Core (see form in appendix E). The data manager assigned to the clinical trial at each site will be responsible for completing the report form. The completed reports will be reviewed and signed off by the site Principal Investigator (PI) or by one of the Co-investigators in the absence of the PI. The signed off forms will then be forwarded to the study coordinator at Karmanos Cancer Institute (coordinating site), for review of completeness and processing with the Data and Safety Monitoring Committee.

The Karmanos Cancer Institute, Data and Safety Monitoring Committee will meet on a regular basis to review the prior Serious Adverse Event forms and Data and Safety Monitoring study specific reports that have been filed.

## APPENDIX A Zubrod/ECOG /KarnofskyPerformance Status Criteria

| **ECOG Performance Status Scale** | | **Karnofsky Performance Scale** |
|---|---|---|
| Descriptions | Percent | Description |
| Normal activity. Fully active, able to carry on all predisease performance without restriction. | 100 | Normal, no complaints, no evidence of disease. |
| | 90 | Able to carry on normal activity; minor signs or symptoms of disease. |
| Symptoms, but ambulatory. Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature (eg, light housework, office work). | 80 | Normal activity with effort; some signs or symptoms of disease. |
| | 70 | Cares for self, unable to carry on normal activity or to do active work. |
| In bed < 50% of the time. Ambulatory and capable of all self-care, but unable to carry out any work activities. Up and about more than 50% of waking hours. | 60 | Requires occasional assistance, but is able to care for most of his/ her needs. |
| | 50 | Requires considerable assistance and frequent medical care. |
| In bed > 50% of the time. Capable of only limited self-care, confined to bed or chair more than 50% of waking hours. | 40 | Disabled, requires special care and assistance. |
| | 30 | Severely disabled, hospitalization indicated. Death not imminent. |
| 100% bedridden. Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair. | 20 | Very sick, hospitalization indicated. Death not imminent. |
| | 10 | Moribund, fatal processes progressing rapidly. |
| Dead | 0 | Dead |

ECOG = Eastern Cooperative Oncology Group.

**APPENDIX B**

**SAMPLE OF DRUG ORDERING AND PHARMACY REFERENCE MATERIAL**

**Nivolumab (BMS-936558) Pharmacy Reference Material**

- Nivolumab has a concentration of 10mg/mL and is provided in a 10mL vial. Ten or five vials are provided in a carton.

***Initial Orders***

- *Following submission and approval of the required regulatory documents, and an executed study agreement, a supply of nivolumab may be ordered by completing a Drug Request Form provided by BMS for this specific trial. The first request may take place upon screening of the first patient*
- *The initial order should be limited to 20 vials. Allow 5 business days for shipment of drug from BMS receipt of the Drug Request Form. Drug is protocol specific, but not patient specific. All drug product will be shipped by courier in a temperature-controlled container. It is possible that sites may have more than one nivolumab clinical study ongoing at the same time. <u>It is imperative that only drug product designated for this protocol number be used for this study.</u>*
- *<u>Pharmacy supplies not provided by BMS:</u> Empty IV bags/containers, approved diluents, In-line filters and infusion tubing*

***Re-Supply***

- *Drug re-supply request form should be submitted electronically 5 business days before the expected delivery date. Deliveries will be made Tuesday through Friday.*
- *When assessing need for resupply, institutions should keep in mind the number of vials used per treatment dose, and that shipments may take upto 14 business days from receipt of request. Drug is not patient-specific. Be sure to check with your pharmacy regarding existing investigational stock to assure optimal use of drug on hand.*

***Drug Excursions***

- *Drug excursions should be reported immediately to BMS on the form provided with the study-specific drug order form*

***Please refer to the most recent version of the Investigator Brochure for additional information.***

**<u>Storage Conditions & Handling:</u>**

- Store at 2-8°C (36-46°F), protect from light, freezing, and shaking.

- If any temperature excursions are encountered during storage, please report these to BMS for assessment via the Temperature Excursion Response Form.
- As with all injectable drugs, care should be taken when handling and preparing nivolumab. Whenever possible, nivolumab should be prepared in a laminar flow hood or safety cabinet using standard precautions for the safe handling of intravenous agents applying aseptic technique.
- Partially used vials should be disposed at the site following procedures for the disposal of anticancer drugs.

After final drug reconciliation, unused nivolumab vials should be disposed at the site following procedures for the disposal of anticancer drugs. For further information, please either discuss with your BMS CSR&O protocol manager or refer to your site IP Destruction policies and procedures

**Use Time/Stability:**

The administration of BMS-936558-01 injection prepared for dosing nivolumab infusion must be completed within 24 hours of preparation. If not used immediately, the infusion solution may be stored up to 20 hours in a refrigerator at under refrigeration conditions (2°-°-8°C (, 36°-46°F) and used within 4 for up to 24 hours, and a maximum of 8 hours of the total 24 hours can be at room temperature (20°-25°C, 68°-77°F) and under room light. The maximum 4-hour period under room temperature and room light conditions for undiluted and diluted solutions of BMS-936558-01 injection in the IV bag should be inclusive of the product administration period.

**Preparation and Administration:**

1. Visually inspect the drug product solution for particulate matter and discoloration prior to administration. Discard if solution is cloudy, if there is pronounced discoloration (solution may have a pale-yellow color), or if there is foreign particulate matter other than a few translucent-to-white, amorphous particles.

   *Note: Mix by **gently** inverting several times. **Do not** shake.*
2. Aseptically withdraw the required volume of nivolumab solution into a syringe, and dispense into an IV. bag. If multiple vials are needed for a subject, it is important to use a separate sterile syringe and needle for each vial to prevent problems such as dulling of needle tip, stopper coring, repeated friction of plunger against syringe barrel wall **Do not** administer study drug as an IV push or bolus injection
3. Add the appropriate volume of 0.9% Sodium Chloride Injection solution or 5% Dextrose Injection solution. *It is acceptable to add nivolumab solution from the vials into an appropriate pre-filled bag of diluent.*

   ***Note: Nivolumab infusion concentration must be at or above the minimum allowable concentration of 0.35 mg/mL [IBV13 Addendum Section 3.2.2]***

   *Note: It is not recommended that so-called "channel" or tube systems are used to transport prepared infusions of nivolumab.*
4. Attach the IV bag containing the nivolumab solution to the infusion set and filter.

5. At the end of the infusion period, flush the line with a sufficient quantity of approved diluents.

**APPENDIX C**

## Important Safety Information for Nivolumab [For the most updated information refer to the package insert of Opdivo/Nivolumab] https://packageinserts.bms.com/pi/pi_opdivo.pdf

**General Guidelines**

- These general guidelines constitute guidance to the Investigator. The guidance applies to all immuno-oncology (I-O) agents and regimens.
- Where applicable the Approved Label should be used for guidance around dose modifications and discontinuation
- A general principle is that differential diagnoses should be diligently evaluated according to standard medical practice. Non-inflammatory etiologies should be considered and appropriately treated.
- Corticosteroids are a primary therapy for immuno-oncology drug-related adverse events. The oral equivalent of the recommended IV doses may be considered for ambulatory patients with low-grade toxicity. The lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of oral corticosteroids.
- Consultation with a medical or surgical specialist, especially prior to an invasive diagnostic or therapeutic procedure, is recommended.
- The frequency and severity of the related adverse events covered by these algorithms will depend on the immuno-oncology agent or regimen being used

Investigators should refer to the most current version of the IB or Approved Label for current recommendations for management of a specific Adverse Event of interest.
Information must be included in the protocol for AE management, modifications and discontinuation. The format should be that which is acceptable per institutional practices or procedures:
Important Safety Information

Immune-Mediated Pneumonitis
Nivolumab can cause immune-mediated pneumonitis. Fatal cases have been reported. Monitor patients for signs with radiographic imaging and for symptoms of pneumonitis. Administer corticosteroids for Grade 2 or more severe pneumonitis. Permanently discontinue for Grade 3 or 4 and withhold until resolution for Grade 2. In patients receiving Nivolumab monotherapy, fatal cases of immune-mediated pneumonitis have occurred. Immune-mediated pneumonitis occurred in 3.1% (61/1994) of patients.

Immune-Mediated Colitis
Nivolumab can cause immune-mediated colitis. Monitor patients for signs and symptoms of colitis. Administer corticosteroids for Grade 2 (of more than 5 days duration), 3, or 4 colitis. Withhold monotherapy for Grade 2 or 3 and permanently discontinue for Grade 4 or recurrent colitis upon re-initiation of Nivolumab. In patients receiving mon Nivolumab otherapy, immune-mediated colitis occurred in 2.9% (58/1994) of patients. In patients who received OPDIVO as a single agent, immune-mediated colitis occurred in 2.9% (58/1994)

of patients; the median time to onset was 5.3 months (range: 2 days to 20.9 months). Immune-mediated colitis led to permanent discontinuation of in nivolumab 0.7% and withholding of OPDIVO in 1% of patients. Approximately 91% of patients with colitis received high-dose corticosteroids (at least 40 mg prednisone equivalents per day) for a median duration of 23 days (range: 1 day to 9.3 months). Four patients required addition of infliximab to high-dose corticosteroids. Complete resolution occurred in 74% of patients. Approximately 16% of patients had recurrence of colitis after re-initiation of nivolumab.

Immune-Mediated Hepatitis

Nivolumab can cause immune-mediated hepatitis. Monitor patients for abnormal liver tests prior to and periodically during treatment. Administer corticosteroids for Grade 2 or greater transaminase elevations. Withhold for Grade 2 and permanently discontinue for Grade 3 or 4 immune-mediated hepatitis.

In patients who received nivolumab as a single agent, immune-mediated hepatitis occurred in 1.8% (35/1994) of patients; the median time to onset was 3.3 months (range: 6 days to 9 months). Immune-mediated hepatitis led to permanent discontinuation of nivolumab in 0.7% and withholding of OPDIVO in 1% of patients. All patients with hepatitis received high-dose corticosteroids (at least 40 mg prednisone equivalents) for a median duration of 23 days (range: 1 day to 2 months). Two patients required the addition of mycophenolic acid to high-dose corticosteroids. Complete resolution occurred in 74% of patients. Approximately 29% of patients had recurrence of hepatitis after re-initiation of nivolumab.

Immune-Mediated Endocrinopathies

Nivolumab can cause immune-mediated hypophysitis, immune-mediated adrenal insufficiency, autoimmune thyroid disorders, and Type 1 diabetes mellitus. Monitor patients for signs and symptoms of hypophysitis, signs and symptoms of adrenal insufficiency, thyroid function prior to and periodically during treatment, and hyperglycemia. Administer hormone replacement as clinically indicated and corticosteroids for Grade 2 or greater hypophysitis. Withhold for Grade 2 or 3 and permanently discontinue for Grade 4 hypophysitis. Administer corticosteroids for Grade 3 or 4 adrenal insufficiency. Withhold for Grade 2 and permanently discontinue for Grade 3 or 4 adrenal insufficiency. Administer hormone-replacement therapy for hypothyroidism. Initiate medical management for control of hyperthyroidism. Withhold for Grade 3 and permanently discontinue for Grade 4 hyperglycemia.

•In patients receiving Nivolumab monotherapy, hypophysitis occurred in 0.6% (12/1994) of patients. In patients receiving nivolumab monotherapy, adrenal insufficiency occurred in 1% (20/1994) of patients. In patients receiving Nivolumab monotherapy, hypothyroidism or thyroiditis resulting in hypothyroidism occurred in 9% (171/1994) of patients. Hyperthyroidism occurred in 2.7% (54/1994) of patients receiving Nivolumab monotherapy. In patients receiving Nivolumab monotherapy, diabetes occurred in 0.9% (17/1994) of patients.

Immune-Mediated Nephritis and Renal Dysfunction

Nivolumab can cause immune-mediated nephritis. Monitor patients for elevated serum creatinine prior to and periodically during treatment. Administer corticosteroids for Grades 2-4 increased serum creatinine. Withhold Nivolumab for Grade 2 or 3 and permanently discontinue for Grade 4 increased serum creatinine. In patients receiving Nivolumab monotherapy, immune-mediated nephritis and renal dysfunction occurred in 1.2% (23/1994) of patients.

Immune-Mediated Skin Adverse Reactions
Nivolumab can cause immune-mediated rash, including Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN), some cases with fatal outcome. Administer corticosteroids for Grade 3 or 4 rash. Withhold for Grade 3 and permanently discontinue for Grade 4 rash. For symptoms or signs of SJS or TEN, withhold Nivolumab and refer the patient for specialized care for assessment and treatment; if confirmed, permanently discontinue. In patients receiving Nivolumab monotherapy, immune-mediated rash occurred in 9% (171/1994) of patients.

Immune-Mediated Encephalitis
Nivolumab can cause immune-mediated encephalitis. Evaluation of patients with neurologic symptoms may include, but not be limited to, consultation with a neurologist, brain MRI, and lumbar puncture. Withhold Nivolumab in patients with new-onset moderate to severe neurologic signs or symptoms and evaluate to rule out other causes. If other etiologies are ruled out, administer corticosteroids and permanently discontinue Nivolumab for immune-mediated encephalitis. In patients receiving Nivolumab monotherapy, encephalitis occurred in 0.2% (3/1994) of patients. Fatal limbic encephalitis occurred in one patient after 7.2 months of exposure despite discontinuation of Nivolumab and administration of corticosteroids.

Other Immune-Mediated Adverse Reactions
Nivolumab can cause other clinically significant and potentially fatal immune-mediated adverse reactions. Immune-mediated adverse reactions may occur after discontinuation of therapy. For any suspected immune-mediated adverse reactions, exclude other causes. Based on the severity of the adverse reaction, permanently discontinue or withhold nivolumab, administer high-dose corticosteroids, and if appropriate, initiate hormone-replacement therapy. Upon improvement to Grade 1 or less, initiate corticosteroid taper and continue to taper over at least 1 month. Consider restarting after completion of corticosteroid taper based on the severity of the event . Across clinical trials of OPDIVO administered as a single agent or in combination with ipilimumab, the following clinically significant immune-mediated adverse reactions, some with fatal outcome, occurred in <1.0% of patients who received nivolumab: myocarditis, rhabdomyolysis, myositis, uveitis, iritis, pancreatitis, facial and abducens nerve paresis, demyelination, polymyalgia rheumatica, autoimmune neuropathy, Guillain-Barré syndrome, hypopituitarism, systemic inflammatory response syndrome, gastritis, duodenitis, sarcoidosis, histiocytic necrotizing lymphadenitis (Kikuchi lymphadenitis), motor dysfunction, vasculitis, aplastic anemia, pericarditis, and myasthenic syndrome. If uveitis occurs in combination with other immune-mediated adverse reactions, consider a Vogt-Koyanagi-Harada-like syndrome,

which has been observed in patients who received nivolumab and may require treatment with systemic steroids to reduce the risk of permanent vision loss.

Infusion Reactions
In patients who received nivolumab as a 60-minute intravenous infusion, infusion-related reactions occurred in 6.4% (127/1994) of patients. In a trial assessing the pharmacokinetics and safety of a more rapid infusion, in which patients received nivolumab as a 60-minute intravenous infusion or a 30-minute intravenous infusion, infusion-related reactions occurred in 2.2% (8/368) and 2.7% (10/369) of patients, respectively. Additionally, 0.5% (2/368) and 1.4% (5/369) of patients, respectively, experienced adverse reactions within 48 hours of infusion that led to dose delay, permanent discontinuation or withholding of nivolumab.

Embryo-Fetal Toxicity
•Based on its mechanism of action, OPDIVO can cause fetal harm when administered to a pregnant woman. Advise pregnant women of the potential risk to a fetus. Advise females of reproductive potential to use effective contraception during treatment with a Nivolumab containing regimen and for at least 5 months after the last dose of Nivolumab.

Lactation
•It is not known whether OPDIVO is present in human milk. Because many drugs, including antibodies, are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from Nivolumab -containing regimen, advise women to discontinue breastfeeding during treatment.

Serious Adverse Reactions
•In Checkmate 017 and 057, serious adverse reactions occurred in 46% of patients receiving Nivolumab (n=418). The most frequent serious adverse reactions reported in at least 2% of patients receiving Nivolumab were pneumonia, pulmonary embolism, dyspnea, pyrexia, pleural effusion, pneumonitis, and respiratory failure.

Common Adverse Reactions
•In Checkmate 017 and 057, the most common adverse reactions (≥20%) in patients receiving Nivolumab (n=418) were fatigue, musculoskeletal pain, cough, dyspnea, and decreased appetite.

## APPENDIX D MANAGEMENT ALGORITHMS

### Dose Modifications for Nivolumab/Opdivo (Package Insert Bristol-Myers Squibb)

Recommendations for OPDIVO modifications are provided in Table below. There are no recommended dose modifications for hypothyroidism or hyperthyroidism. Interrupt or slow the rate of infusion in patients with mild or moderate infusion reactions. Discontinue OPDIVO in patients with severe or life-threatening infusion reactions.

| **Recommended Dose Modifications for** Nivolumab **Adverse Reaction** | **Severity*** | **Dose Modification** |
|---|---|---|
| Grade 4 diarrhea or colitis | Permanently discontinue | |
| Pneumonitis | Grade 2 pneumonitis | Withhold dose (a) |
| | Grade 3 or 4 pneumonitis | Permanently discontinue |
| Hepatitis | Aspartate aminotransferase (AST)/or alanine aminotransferase (ALT) more than 3 and up to 5 times the upper limit of normal or total bilirubin more than 1.5 and up to 3 times the upper limit of normal | Withhold dose (a) |
| | AST or ALT more than 5 times the upper limit of normal or total bilirubin more than 3 times the upper limit of normal | Permanently discontinue |
| Hypophysitis | Grade 2 or 3 hypophysitis | Withhold dose (a ) |
| | Grade 4 hypophysitis | Permanently discontinue |
| Adrenal Insufficiency | Grade 2 adrenal insufficiency | Withhold dose (a) |
| | Grade 3 or 4 adrenal insufficiency | Permanently discontinue |
| Type 1 Diabetes Mellitus | Grade 3 hyperglycemia | Withhold dose (a) |
| | Grade 4 hyperglycemia | Permanently discontinue |
| Nephritis and Renal Dysfunction | Serum creatinine more than 1.5 and up to 6 times the upper limit of normal | Withhold dose (a ) |
| | Serum creatinine more than 6 times the upper limit of normal | Permanently discontinue |
| Skin | Grade 3 rash or suspected Stevens-Johnson syndrome (SJS) or toxic epidermal necrolysis (TEN) | Withhold dose (a) |
| | Grade 4 rash or confirmed SJS or TEN | Permanently discontinue |
| Encephalitis | New-onset moderate or severe neurologic signs or symptoms | Withhold dose (a ) |
| | Immune-mediated encephalitis | Permanently discontinue |
| Other | Other Grade 3 adverse reaction First occurrence Recurrence of same Grade 3 adverse reactions | Withhold dose (a )Permanently discontinue |
| | Life-threatening or Grade 4 adverse reaction | Permanently discontinue |
| | Requirement for 10 mg per day or greater prednisone or equivalent for more than 12 weeks | Permanently discontinue |
| | Persistent Grade 2 or 3 adverse reactions lasting 12 weeks or longer | Permanently discontinue |

* Toxicity was graded per National Cancer Institute Common Terminology Criteria for Adverse Events. Version 4.0 (NCI CTCAE v4). a Resume treatment when adverse reaction improves to Grade 0 or 1.

## APPENDIX E

## Barbara Ann Karmanos Cancer Institute Data and Safety Monitoring Report

**PROTOCOL#:** _____ **REPORT DATE:** _____

| **PROTOCOL TITLE** | | | |
|---|---|---|---|
| | | | |
| **ATTENDANCE** | | | |
| | | | |
| | | | |
| **PROTOCOL ACTIVITY SINCE LAST REPORT** | | | |
| Accrual Goal: | Eligible: | | Total number of AE's to date: |
| Accrual to Date: | Ineligible:<br>(provide reason): | | |
| Accrual Since<br>Last Monthly Report: | | | |

| SPECIFICALLY FOR PHASE I TRIAL &/OR DOSE ESCALATING TRIALS: | |
|---|---|
| DOSE LEVEL | ACCRUAL |
| | |
| | |

**RECORD ALL GRADE 3, 4, AND 5 ADVERSE EVENTS (AE). GROUP BY CATEGORY OF AE. RECORD THE DATE OF THE OCCURRENCE, ATTRIBUTION AND IF REPORTABLE TO THE IRB. SHADE THE ROWS OF THE AE'S THAT HAVE OCCURRED FOR THIS REPORT. ATTACH THE HIC UP REPORT FORM FOR THESE REPORTABLE EVENTS THAT OCCURRED ON THIS REPORT.**

| Pt. ID# | Category and type of adverse reaction | Date of Occurrence | Grade[1] | Attribution[2] | Reportable to IRB (Y/N) Yes with date |
|---|---|---|---|---|---|
| | | | | | |
| | | | | | |
| | | | | | |

1. Grade: 1-Mild, 2-Moderate, 3- Severe, 4-Life-threatening, or 5- Death.
2. Attribution: 1-unrelated, 2 - unlikely, 3 - possibly, 4 - probably, or 5 - definitely

| **OFF TREATMENT □ Provide reason [progression, death, toxicity, completed therapy, etc].** | | | |
|---|---|---|---|
| | | | |
| **PROTOCOL VIOLATIONS □ Deviations from protocol treatment, monitoring, or study calendar.** | | | |
| | | | |
| **PROTOCOL AMENDMENTS □ Include date submitted to regulatory bodies and date approved.** | | | |
| | | | |
| **OTHER COMMENTS** | | | |
| | | | |
| **Investigator Signature:** | | **Data Manager Signature:** | |

## APPENDIX F

FACT-IT and BISI Questionnaires

Below is a list of statements that other people with your illness have said are important. **Please circle or mark one number per line to indicate your response as it applies to the <u>past 7 days</u>.**

| | | Not at all | A little bit | Some-what | Quite a bit | Very much |
|---|---|---|---|---|---|---|
| GP4 | I have pain ..... | 0 | 1 | 2 | 3 | 4 |
| GP1 | I have a lack of | 0 | 1 | 2 | 3 | 4 |

| | | | | | | |
|---|---|---|---|---|---|---|
| C2 | I am losing weight ..... | 0 | 1 | 2 | 3 | 4 |
| GP2 | I have | 0 | 1 | 2 | 3 | 4 |
| GP6 | I feel | 0 | 1 | 2 | 3 | 4 |
| GE6 | I worry that my condition will get | 0 | 1 | 2 | 3 | 4 |
| BL1 | I have trouble controlling my urine | 0 | 1 | 2 | 3 | 4 |

| | **PHYSICAL WELL-BEING** | **Not at all** | **A little bit** | **Some-what** | **Quite a bit** | **Very much** |
|---|---|---|---|---|---|---|
| GP1 | I have a lack of energy ..... | 0 | 1 | 2 | 3 | 4 |
| GP2 | I have nausea ..... | 0 | 1 | 2 | 3 | 4 |
| GP3 | Because of my physical condition, I have trouble meeting the needs of my family ..... | 0 | 1 | 2 | 3 | 4 |
| GP4 | I have pain ..... | 0 | 1 | 2 | 3 | 4 |
| GP5 | I am bothered by side effects of treatment ..... | 0 | 1 | 2 | 3 | 4 |
| GP6 | I feel ill ..... | 0 | 1 | 2 | 3 | 4 |
| GP7 | I am forced to spend time in bed | 0 | 1 | 2 | 3 | 4 |

## SOCIAL/FAMILY WELL-BEING

| | | Not at all | A little bit | Some-what | Quite a bit | Very much |
|---|---|---|---|---|---|---|
| GS1 | I feel close to my friends | 0 | 1 | 2 | 3 | 4 |
| GS2 | I get emotional support from my family | 0 | 1 | 2 | 3 | 4 |
| GS3 | I get support from my friends | 0 | 1 | 2 | 3 | 4 |
| GS4 | My family has accepted my illness | 0 | 1 | 2 | 3 | 4 |
| GS5 | I am satisfied with family communication about my illness | 0 | 1 | 2 | 3 | 4 |
| GS6 | I feel close to my partner (or the person who is my main support) | 0 | 1 | 2 | 3 | 4 |
| Q1 | *Regardless of your current level of sexual activity, please answer the following question. If you prefer not to answer it, please mark this box* ☐ *and go to the next section.* | | | | | |
| GS7 | I am satisfied with my sex life | 0 | 1 | 2 | 3 | 4 |

**Please circle or mark one number per line to indicate your response as it applies to the <u>past 7 days</u>.**

| | **EMOTIONAL WELL-BEING** | **Not at all** | **A little bit** | **Some-what** | **Quite a bit** | **Very much** |
|---|---|---|---|---|---|---|
| GE1 | I feel sad | 0 | 1 | 2 | 3 | 4 |
| GE2 | I am satisfied with how I am coping with my illness | 0 | 1 | 2 | 3 | 4 |
| GE3 | I am losing hope in the fight against my illness | 0 | 1 | 2 | 3 | 4 |
| GE4 | I feel nervous | 0 | 1 | 2 | 3 | 4 |
| GE5 | I worry about dying | 0 | 1 | 2 | 3 | 4 |
| GE6 | I worry that my condition will get | 0 | 1 | 2 | 3 | 4 |

| | **FUNCTIONAL WELL-BEING** | **Not at all** | **A little bit** | **Some-what** | **Quite a bit** | **Very much** |
|---|---|---|---|---|---|---|
| GF1 | I am able to work (include work at home) | 0 | 1 | 2 | 3 | 4 |
| GF2 | My work (include work at home) is fulfilling | 0 | 1 | 2 | 3 | 4 |
| GF3 | I am able to enjoy life | 0 | 1 | 2 | 3 | 4 |

| | | | | | | |
|---|---|---|---|---|---|---|
| GF4 | I have accepted my illness | 0 | 1 | 2 | 3 | 4 |
| GF5 | I am sleeping well | 0 | 1 | 2 | 3 | 4 |
| GF6 | I am enjoying the things I usually do for fun | 0 | 1 | 2 | 3 | 4 |
| GF7 | I am content with the quality of my life right | 0 | 1 | 2 | 3 | 4 |

**Bladder Symptom Index Questionnaire**

**Please circle or mark one number per line to indicate your response as it applies to the <u>past 7 days</u>.**

| | **ADDITIONAL CONCERNS** | **Not at all** | **A little bit** | **Some-what** | **Quite a bit** | **Very much** |
|---|---|---|---|---|---|---|
| BL1 | I have trouble controlling my urine | 0 | 1 | 2 | 3 | 4 |
| C2 | I am losing weight | 0 | 1 | 2 | 3 | 4 |
| C3 | I have control of my bowels | 0 | 1 | 2 | 3 | 4 |
| BL2 | I urinate more frequently than usual | 0 | 1 | 2 | 3 | 4 |
| C5 | I have diarrhea (diarrhoea) | 0 | 1 | 2 | 3 | 4 |
| C6 | I have a good appetite | 0 | 1 | 2 | 3 | 4 |
| C7 | I like the appearance of my | 0 | 1 | 2 | 3 | 4 |
| BL3 | It burns when I urinate | 0 | 1 | 2 | 3 | 4 |
| BL4 | I am interested in sex | 0 | 1 | 2 | 3 | 4 |
| BL5 | (For men only) I am able to have and maintain an erection | 0 | 1 | 2 | 3 | 4 |

| | | | | | | |
|---|---|---|---|---|---|---|
| Q2 | Do you have an ostomy appliance?<br>No___ Yes___ If yes, answer the following two items:<br>↓ | | | | | |
| C8 | I am embarrassed by my ostomy appliance<br>..... | 0 | 1 | 2 | 3 | 4 |
| C9 | Caring for my ostomy appliance is difficult<br>..... | 0 | 1 | 2 | 3 | 4 |

**APPENDIX G**

Please refer to Lab Manual for Specimen collection, Processing and Shipping instructions if applicable.

Please notify Dr. Parajuli when sending samples. Contact info:

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