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Clinical Protocol CA209274

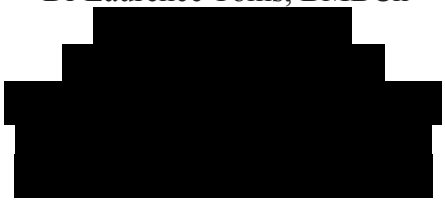
A Phase 3 Randomized, Double-blind, Multi-center Study of Adjuvant Nivolumab versus Placebo in Subjects with High Risk Invasive Urothelial Carcinoma

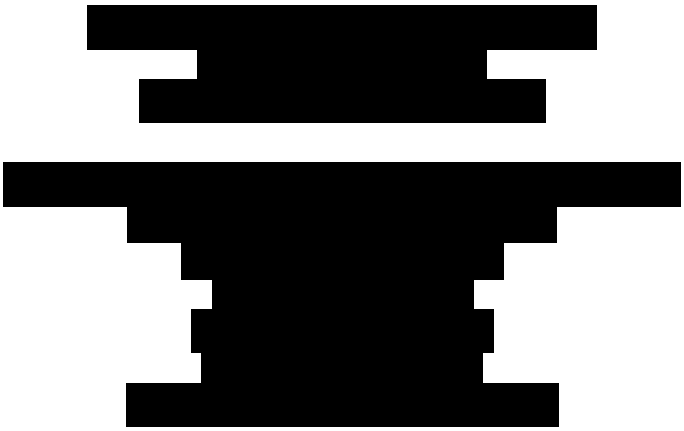
(CheckMate 274: CHECKpoint pathway and nivolu**MAb** clinical **T**rial **E**valuation **274)**

Revised Protocol Number: 05
Incorporates Administrative Letter: 07

Study Director/Medical Monitor

Dr Laurence Toms, BMBCh





study. Any permitted disclosures will be made only on a confidential "need to know" basis within your organization or to your independent ethics committee(s). Any other use, copying, disclosure or dissemination of this information is strictly prohibited unless expressly authorized in writing by BMS. Any supplemental information (eg, amendments) that may be added to this document is also confidential and proprietary to BMS and must be kept in confidence in the same manner as the contents of this document. Any person who receives this document without due authorization from BMS is requested to return it to BMS or promptly destroy it. All other rights reserved. References to BMS in this protocol may apply to partners to which BMS has transferred obligations, eg, a Contract Research Organization (CRO).

DOCUMENT HISTORY

Document	Date of Issue	Summary of Change
Revised Protocol 05	18-Oct-2019	Major changes • Addition of formal interim overall survival (OS) analyses at the time of final disease free survival (DFS) analysis for each of the 2 populations specified in the primary objective. • Appendix 1: Algorithms For Management of Side Effects has been updated. • Administrative Letter 07 clarifications have been incorporated.
Administrative Letter 07	08-Jul-2019	Clarifies study time periods during which protocol-specified concomitant medications are prohibited.
Revised Protocol 04	19-Dec-2018	Incorporates Amendment 15 and Administrative Letters: 01, 02, 03, 04 and 05
Amendment 15	19-Dec-2018	Incorporates statistical modifications, removal of the cap on PD-L1, [redacted] Revisions to Inclusion and Exclusion Criteria; and timing of TSH laboratory tests. Updates to the most recent guidance for nivolumab treatment. Minor formatting and typographical corrections were corrected.
Administrative Letter 05	11-Sep-2018	[redacted]
Administrative Letter 04	15-Jun-2018	Change in study personnel.
Administrative Letter 03	21-Feb-2018	Change in study personnel.
Administrative Letter 02	21-Apr-2017	Change in study personnel.
Administrative Letter 01	12-Jan-2017	Change in study personnel.
Revised Protocol 03	18-Jul-2017	Incorporates Amendment 12
Amendment 12	18-Jul-2017	Provides a more precise description of low- and high-risk non-muscle invasive bladder cancer (NMIBC) conforming to nomenclature used in the 1973 WHO and 2004 WHO/ISUP guidelines; aligns the synopsis with the body of the protocol with respect to non-eligibility of subjects with high-risk NMIBC; states that subjects with CIS at urethral or ureteral surgical margins are not eligible for study; changes the PD-L1-positive percentage from 50% to 46% in accord with recently published data from the CA209-275 registrational study; applies a 20% cap on the number of pelvis and ureter cancer subjects randomized to the study; states that suspect lesions observed during screening procedures must be discussed with the MM prior to randomization; other minor changes.
Revised Protocol 02	18-Aug-2016	Incorporates Amendment 10
Amendment 10	18-Aug-2016	Extends acceptable period of time between radical resection and randomization from 90 days to 120 days; clarifies pathology language for eligibility; clarifies recurrence language, updates safety and contraceptive language to be consistent with nivolumab Investigators Brochure version 15; other minor changes.
Revised Protocol 01	21-Oct-2015	Incorporates Amendment 03

Document	Date of Issue	Summary of Change
Amendment 03	21-Oct-2015	Modified randomization rate from 2:1 to 1:1; increased total number of treated subjects from 600 to 640; other minor changes, including simplifying the description of the study population and definition of recurrences.
Original Protocol	15-Jul-2015	Not applicable

SYNOPSIS

Clinical Protocol CA209274

Protocol Title: A Phase 3 Randomized, Double-blind, Multi-center Study of Adjuvant Nivolumab versus Placebo in Subjects with High Risk Invasive Urothelial Carcinoma

(CheckMate 274: CHECKpoint pathway and nivoluMAb clinical Trial Evaluation 274)

Investigational Product(s), Dose and Mode of Administration, Duration of Treatment with Investigational Product(s):

Nivolumab monotherapy or placebo administered IV at 240 mg every 2 weeks until recurrence, unacceptable toxicity or discontinuation from study for a maximum of 1 year.

Study Phase: 3

Research Hypothesis: Treatment with nivolumab will extend disease-free survival, compared with placebo, as adjuvant therapy in all randomized patients and in patients with PD-L1 expressing tumors (membranous staining in ≥ 1%) who are at high risk of recurrence after undergoing radical resection of invasive urothelial carcinoma (IUC).

Objectives:

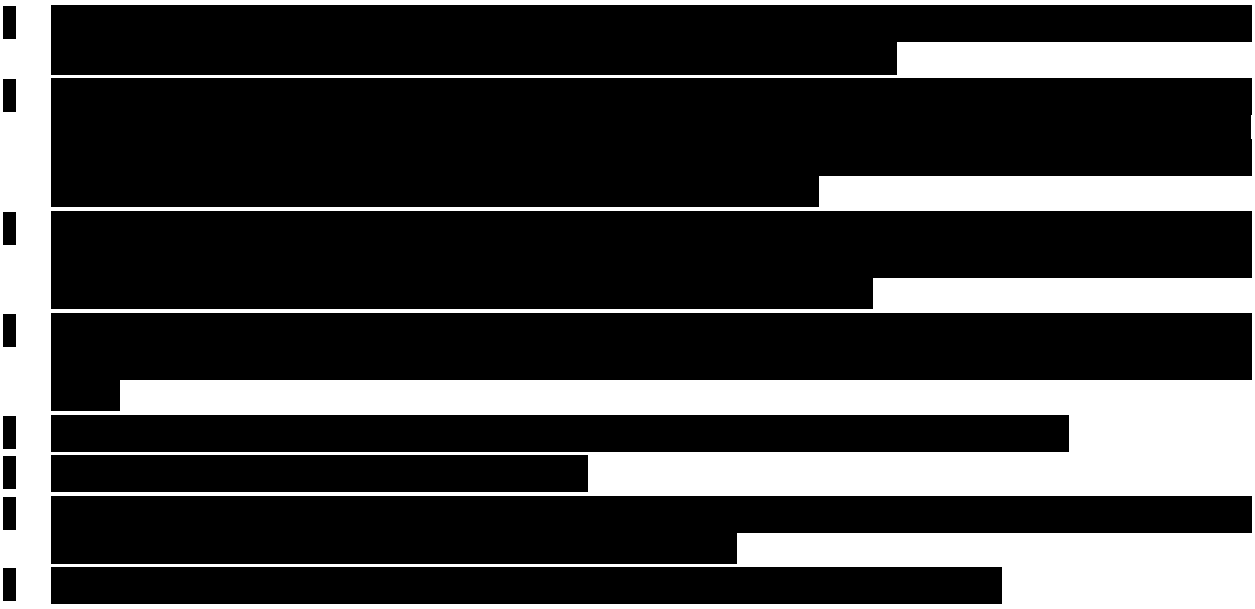
Co-Primary Objectives

- To compare the DFS for nivolumab versus placebo in subjects with tumors expressing PD L1 (≥ 1% membranous staining in tumor cells) and all randomized subjects

Secondary Objectives

- To compare the overall survival (OS) for nivolumab versus placebo in subjects with tumors expressing PD-L1 (≥ 1% membranous staining in tumor cells) and all randomized subjects.
- To evaluate non-urothelial tract recurrence free survival (NUTRFS) in each randomized treatment group (nivolumab versus placebo) in subjects with tumors expressing PD-L1 (≥ 1% membranous staining in tumor cells) and all randomized subjects
- To evaluate disease specific survival (DSS) in each randomized treatment group (nivolumab and placebo) in subjects with tumors expressing PD-L1 (≥ 1% membranous staining in tumor cells) and all randomized subjects

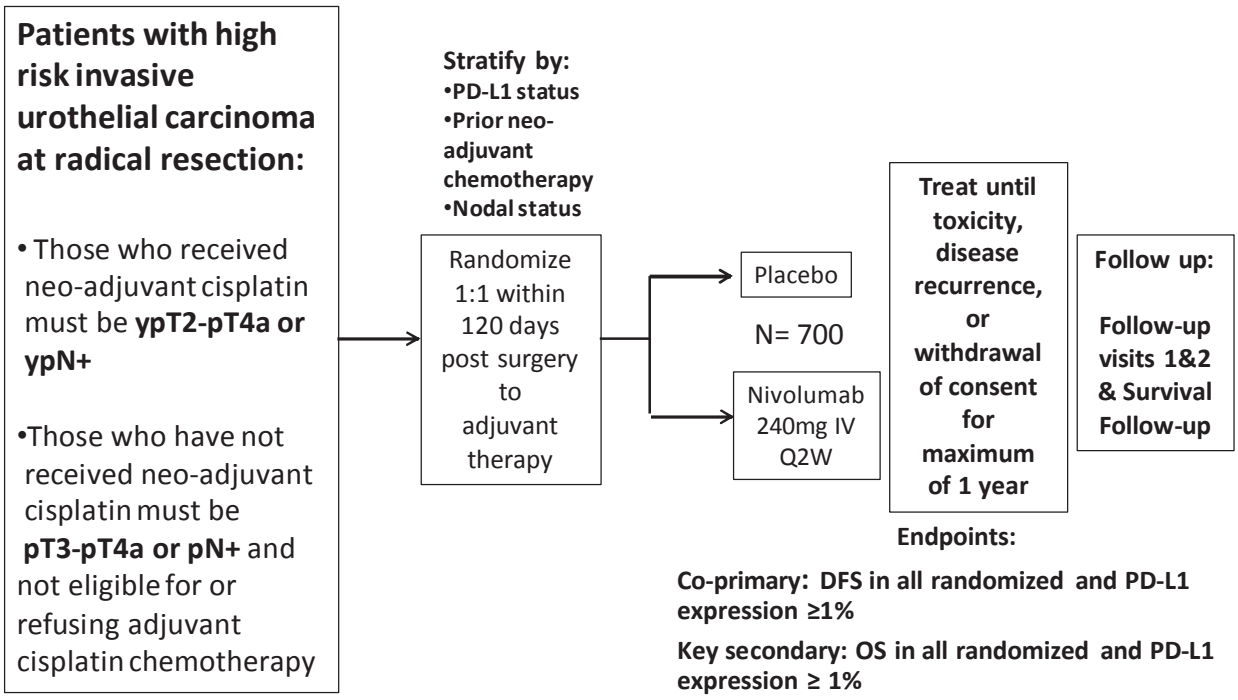
[redacted]



Study Design: This is a phase 3, randomized, double-blind, multicenter trial of adjuvant nivolumab versus placebo in adult male or female subjects who have undergone radical resection of IUC originating in the bladder or upper urinary tract (renal pelvis or ureter) and are at high risk of recurrence:

- Subjects who received neo-adjuvant cisplatin chemotherapy: ypT2-pT4a or ypN+
- Subjects who have not received neo-adjuvant cisplatin chemotherapy: pT3-pT4a or pN+ and are not eligible for or refusing adjuvant cisplatin chemotherapy
- Approximately 700 subjects will be randomized in a blinded fashion 1:1 to nivolumab versus placebo within 120 days of radical resection and stratified by pathologic nodal status (N+ vs. N0/x with < 10 nodes removed vs. N0 with ≥ 10 nodes removed), tumor PD-L1 expression (≥ 1%, < 1%/indeterminate), and use of cisplatin neo-adjuvant chemotherapy. Treatment, in the absence of prohibitive toxicities, disease recurrence/progression, or withdrawal of consent will be continued for a maximum of 1 year. The co-primary endpoint is DFS in subjects with tumors expressing PD-L1 at ≥ 1% (2.5% alpha) and in all randomized subjects (2.5% alpha). The overall sample size is set up to allow a clinically meaningful effect to be statistically significant at alpha level of 2.5% (two-sided) in the all randomized group. Even weighting of the alpha distribution between DFS assessment in all randomized (N = 700) and PD-L1 expressers (~ 42% of the all randomized population) reflects an assumption of enrichment of nivolumab efficacy in the PD-L1 expressers. At the time of the original study design, the anticipated prevalence of PD-L1 + was 46% and the PD-L1-ve population in the study was capped at 54%. During the execution of the study the PD-L1+ rate was ≈42%, for this reason in revised protocol 04 the cap was removed to make the study sample representative of the study population. Hence, it is anticipated that the final population will include approximately 42% of patients who are PD-L1+. The number of randomized subjects with upper tract urothelial cancers (UTUC) will be capped at approximately 20% (140 subjects) of total global enrollment. Once approximately 140 subjects with UTUC are randomized, only subjects with bladder cancer will be enrolled.
- Following discontinuation of study therapy, subjects will be followed for survival and those that have not had a non-urothelial tract recurrence will be followed for recurrence.

Study Design Schematic*



* Note that Per Revised Protocol 04, there is no longer a cap on the number of subjects with PD-L1 expression < 1%.

Study Population: Subjects who have undergone radical resection of IUC originating in the bladder or upper urinary tract (renal pelvis or ureter) and are at high risk of recurrence. Subjects must meet all eligibility criteria specified in Sections 3.3.1 and 3.3.2 of the protocol, including the following

Key Inclusion Criteria (see Protocol Section 3.3.1 for full list of criteria):

1. All subjects must be status post radical surgical resection (R0) for IUC performed within 120 days prior to randomization. Subjects with carcinoma in situ in ureteral or urethral margins are not eligible for study entry.
2. All subjects must have pathologic evidence of urothelial carcinoma (originating in bladder, ureter, or renal pelvis) at high risk of recurrence based on pathologic staging of radical surgery tissue as described in one of the two below scenarios (i or ii):
   i) Subjects who have not received neo-adjuvant cisplatin chemotherapy: pT3-pT4a or pN+ and are not eligible for or refusing adjuvant cisplatin chemotherapy
      (1). Subjects ineligible for cisplatin due to any of the following criteria:
         a. Creatinine Clearance (using the Cockcroft-Gault formula): < 60 mL/min
         b. CTCAE version 4, grade 2 or above audiometric hearing loss
         c. CTCAE version 4, grade 2 peripheral neuropathy
         d. ECOG PS 2
         e. New York Heart Association (NYHA) Class III or IV Heart Failure
      (2). Subjects that are eligible for cisplatin may be candidates if they refuse available adjuvant chemotherapy, despite being informed by the investigator about the treatment options. The subject's refusal must be thoroughly documented.

ii) Subjects who received cisplatin based neo-adjuvant chemotherapy: ypT2-pT4a or ypN+

3. Dominant component of histology needs to be urothelial carcinoma or transitional cell carcinoma. Foci of varied histologies (eg, minor variants) are accepted.
4. All subjects must have disease-free status defined as no clinical or radiographic evidence of recurrence of disease documented by a complete physical examination and imaging studies within 4 weeks of randomization. Subjects with equivocal nodes less than 15 mm in short axis may be eligible after discussion with BMS Medical Monitor. All suspect lesions identified during screening radiographic procedures should be discussed with the Medical Monitor prior to randomization.
   i) Imaging studies must include CT of chest and CT or MRI of abdomen, pelvis, and all known sites of resected disease including cystoscopy in subjects with upper GU primaries who still have bladder intact. Brain imaging (MRI except where contraindicated in which CT scan is acceptable) must be completed within 4 weeks prior to randomization for subjects with clinical suspicion of CNS disease.
   ii) Subjects who are found to have high-risk NMIBC at the time of screening are not eligible for study entry. Patients with low-risk papillary lesions may enter the study if rendered free of disease at cystoscopy. Subjects with intermediate-risk NMIBC may enter the study if intravesical chemotherapy or BCG is not required. Screening cystoscopy may occur within 60 days of randomization and is encouraged to be done prior to other imaging. Any suspect lesions seen on cystoscopy should be biopsied to rule-out the possibility of high-risk lesions.

   Low-risk NMIBC is defined as low-grade lesions or papillary urothelial neoplasms of low malignant potential (PUNLMP; WHO/ISUP 2004 grading system), or TaG1 lesions (WHO 1973 grading system) that are less than 3 cm in diameter.
   High-risk NMIBC is defined as any T1 lesion, any lesion containing carcinoma in situ (CIS) either alone or concomitantly with papillary disease (e.g. CIS with Ta/T1 lesions), and any Ta high-grade (TaHG; WHO/ISUP 2004 grading system) or TaG3 (WHO 1973 grading system) lesion.
   Intermediate-risk NMIBC is defined as lesions not meeting the criteria of high-risk or low-risk.

5. Tumor tissue from the most recently resected site of disease (preferable) or from the transurethral resection that yielded the initial muscle invasive diagnosis must be provided for biomarker analyses. In order to be randomized, a subject must have a PD-L1 expression level classification (≥ 1%, < 1%, indeterminate) as determined by the central lab. If insufficient tumor tissue content is provided for analysis (eg, unevaluable), acquisition of additional archived tumor tissue from the most recent resection (preferable) or from the transurethral resection that yielded the initial muscle invasive diagnosis is required.
6. Life expectancy ≥ 6 months
7. Eastern Cooperative Oncology Group (ECOG) performance status (PS) 0 or 1. Per inclusion 2 i) (1), ECOG PS 2 is listed as part of cisplatin ineligibility criteria. Subjects who have not received cisplatin based neoadjuvant chemotherapy and are considered ineligible for cisplatin adjuvant chemotherapy, may enter the study with ECOG PS 2 (see Appendix 2)
8. Prior surgery that required general anesthesia must be completed at least 4 weeks before study drug administration. Surgery requiring local/epidural anesthesia must be completed at least 72 hours before study drug administration. TURBT must be completed 14 days before randomization.

Key Exclusion Criteria (see Protocol Section 3.3.2 for full list of criteria):

1. Partial cystectomy in the setting of bladder cancer primary tumor or partial nephrectomy in the setting of renal pelvis primary tumor.
2. Adjuvant systemic or radiation therapy for urothelial or prostatic carcinoma following radical surgical resection of urothelial carcinoma.
3. Any serious or uncontrolled medical disorder that, in the opinion of the investigator, may increase the risk associated with study participation or study drug administration, impair the ability of the subject to receive protocol therapy, or interfere with the interpretation of study results.
4. Prior malignancy active within the previous 3 years except for locally curable cancers that have been apparently cured, such as basal or squamous cell skin cancer, prostate cancer with evidence of undetectable Prostate

Specific Antigen (PSA) or carcinoma in situ of the prostate, cervix or breast. Patients with known history of recent metastatic urothelial carcinoma will be excluded.

5. Subjects with active, known or suspected autoimmune disease. Subjects with vitiligo, type I diabetes mellitus, residual hypothyroidism due to autoimmune condition only requiring hormone replacement, psoriasis not requiring systemic treatment, or conditions not expected to recur in the absence of an external trigger are permitted to enroll.
6. Subjects with a condition requiring systemic treatment with either corticosteroids (> 10 mg daily prednisone equivalents) or other immunosuppressive medications within 14 days of study drug administration. Inhaled or topical steroids and adrenal replacement doses > 10 mg daily prednisone equivalents are permitted in the absence of active autoimmune disease.
7. Subjects with history of life-threatening toxicity related to prior immune therapy (eg. anti-CTLA-4 or anti-PD-1/PD-L1 treatment or any other antibody or drug specifically targeting T-cell co-stimulation or immune checkpoint pathways) except those that are unlikely to re-occur with standard countermeasures (eg, hormone replacement after adrenal crisis).
8. All toxicities attributed to prior anti-cancer therapy other than nephropathy, neuropathy, hearing loss, alopecia and fatigue must have resolved to Grade 1 (NCI CTCAE version 4) or baseline before administration of study drug. Subjects with toxicities attributed to prior anti-cancer therapy which are not expected to resolve and result in long lasting sequelae, such as neuropathy after platinum based therapy, are permitted to enroll. See protocol inclusion criterion 2) i) (5) for renal function eligibility. Neuropathy must have resolved to Grade 2 (NCI CTCAE version 4).
9. Treatment with any chemotherapy, radiation therapy, biologics for cancer, intravesical therapy, or investigational therapy within 28 days of first administration of study treatment.

Study Drug: includes both Investigational [Medicinal] Products (IP/IMP) and Non-investigational [Medicinal] Products (Non-IP/Non-IMP) as listed:

Nivolumab (or placebo) dosing				
Drug	**Dose**	**Frequency of administration**	**Route of administration**	**Duration**
Nivolumab (or placebo)	240 mg	every 2 weeks	Intravenous (IV) infusion	Until recurrence or discontinuation from study for a maximum of 1 year

Study Assessments: Baseline disease assessments should be performed within 28 days prior to randomization utilizing CT or MRI. In addition to chest, abdomen, pelvis, upper urinary tract, and all known sites of resected disease (including cystoscopy in subjects with upper GU primaries who still have bladder intact) should be assessed at baseline. Brain imaging (MRI except where contraindicated in which CT scan is acceptable) must be completed within 28 days prior to randomization for subjects with clinical suspicion of CNS disease at screening. Subjects will be evaluated for presence or continued lack of tumor until non-urothelial tract recurrence as below:

- Non-cystoscopy tumor imaging assessments will occur every 12 weeks from the date of first dose to Week 96 (ie, Week 12, 24, 36, 48, 60, 72, 84, 96; +/- 1 week), then every 16 weeks from Week 96 to Week 160 (ie, Week 112, 128, 144, 160; +/- 2 weeks), then every 24 weeks until non-urothelial tract recurrence or treatment is discontinued (whichever occurs later) for a maximum of 5 years (ie, Week 184, 208, 232, 256, +/- 4 weeks).
- Non-cystoscopy tumor imaging assessments: CT of chest, and CT or MRI of abdomen, pelvis, upper urinary tract, and all known sites of disease. Use same imaging method as was used at screening/baseline.
- Cystoscopy in subjects with upper GU primaries who still have bladder intact will occur in addition to other tumor imaging assessments every 12 weeks from the date of first dose to Week 48 (ie, Week 12, 24, 36, 48 +/- 1 week), then every 24 weeks from Week 48 to Week 96 (ie, Week 72, 96; +/- 2 weeks), then every

48 weeks until non-urothelial tract recurrence or treatment is discontinued (whichever occurs later) for a maximum of 5 years (ie, Week 96, 144, 192, 240; +/- 4 weeks).

Statistical Considerations:

Sample Size: The sample size for this study is based on a comparison of the DFS distribution between subjects randomized to receive nivolumab and subjects randomized to receive placebo There will be two co-primary comparisons: in subjects with PD-L1 expression level ≥ 1% and in all randomized subjects with an alpha allocation of 2.5% (two-sided) each.

Approximately 700 subjects will be randomized in 1:1 ratio to nivolumab arm and control arm respectively.

- Approximately 410 DFS events in all randomized subjects will provide around 87% power to detect an average HR of 0.72 with an overall type I error of 2.5% (two-sided)
- Approximately162 DFS events in subjects with PD-L1 expression level ≥ 1% (~ 294 subjects) will provide around 80% power to detect an average HR of 0.61 with an overall type I error of 2.5% (two-sided).

The target average hazard ratios were obtained via simulation using exponential cure rate modeling.

An interim DFS analysis will also be performed when 85% of DFS events in each population will be observed (ie, 348 and 137 DFS events in all randomized and in subjects with PD-L1 expression level ≥ 1%, respectively). The alpha level for DFS will be adjusted for the planned interim analysis using Lan-DeMets alpha spending function with the O'Brien-Fleming type of boundary in East v6.

Assuming an average accrual rate of 16 subjects per month, the accrual will take approximately 43 months. The total duration of the study from start of randomization to final analysis of DFS is expected to be 60 months (43 months of accrual + 17 months of follow-up). DFS analyses in all randomized population and in subjects with PD-L1 expression level ≥ 1% are projected to occur 45 months after start of the study for the interim analyses and 60 months (43 months of accrual + 17 months of follow-up) for the final analyses.

Endpoints: The primary endpoint of DFS will be programmatically determined based on the disease recurrence date provided by the investigator and is defined as the time between the date of randomization and the date of first recurrence (local urothelial tract, local non-urothelial tract or distant) or death (of any cause), whichever occurs first. (Note: a subject who dies without reported recurrence will be considered to have recurred on the date of death.) For subjects who remain alive and whose disease has not recurred, DFS will be censored on the date of last evaluable disease assessment.

Surveillance assessments will occur as stated in the study assessments section above.

This endpoint will be analyzed in two different populations (co-primary): Subjects with PD-L1 expression level ≥ 1% and all randomized subjects.

Analyses: DFS distribution in all randomized subjects and subjects with PD-L1expression level ≥ 1% will be compared between treatment group using a two-sided stratified log-rank test at the overall significance level of 2.5% (two-sided) each.

The HR and corresponding two-sided 100x (1-adjusted α) % confidence intervals (CIs) will be estimated in a Cox proportional hazards model using treatment as a single covariate, stratified by PD-L1 status (only in the all randomized population comparison), prior neo-adjuvant cisplatin chemotherapy, positive lymph node status.

DFS curves will be estimated using the KM product-limit method. Median DFS and the corresponding two-sided 95% CIs using the log-log transformation will be computed. In addition, DFS rate at 6 months, 1 year and 2 years (and yearly after depending on the follow-up) and the corresponding two-sided 95% CIs using the log-log transformation will be computed.

The analyses for secondary endpoint of NUTRFS, DSS and OS will be performed in all randomized subjects as well as in subjects with PD-L1 expression level ≥ 1%. The key secondary OS distribution will be compared between

treatment groups using a two-sided stratified log-rank test at the overall significance level of 2.5% (two-sided) each. These comparisons will be tested using hierarchical procedure in each population.

The OS HR and corresponding two-sided 100x (1-adjusted α)% confidence intervals (CIs) will be estimated in a Cox proportional hazards model using treatment as a single covariate, stratified by PD-L1 status (only in the all randomized population comparison), prior neo-adjuvant cisplatin chemotherapy, positive lymph node status.

The NUTRFS HR and corresponding two-sided 95% CIs will be estimated in a Cox proportional hazards model using treatment as a single covariate, stratified by PD-L1 status (only in the all randomized population comparison), prior neo-adjuvant cisplatin chemotherapy, positive lymph node status.

NUTRFS and OS distribution curves will be estimated using Kaplan-Meier methodology by treatment arm. Median values and the corresponding two-sided 95% CIs using the log-log transformation will also be computed. NUTRFS and OS rates at 6 months, 1 year and 2 years (and yearly after depending on the follow-up) and the corresponding two-sided 95% CIs using the log-log transformation will be computed.

Cumulative incidence of DSS will be also estimated.

No formal comparison will be done for NUTRFS and DSS secondary endpoints.

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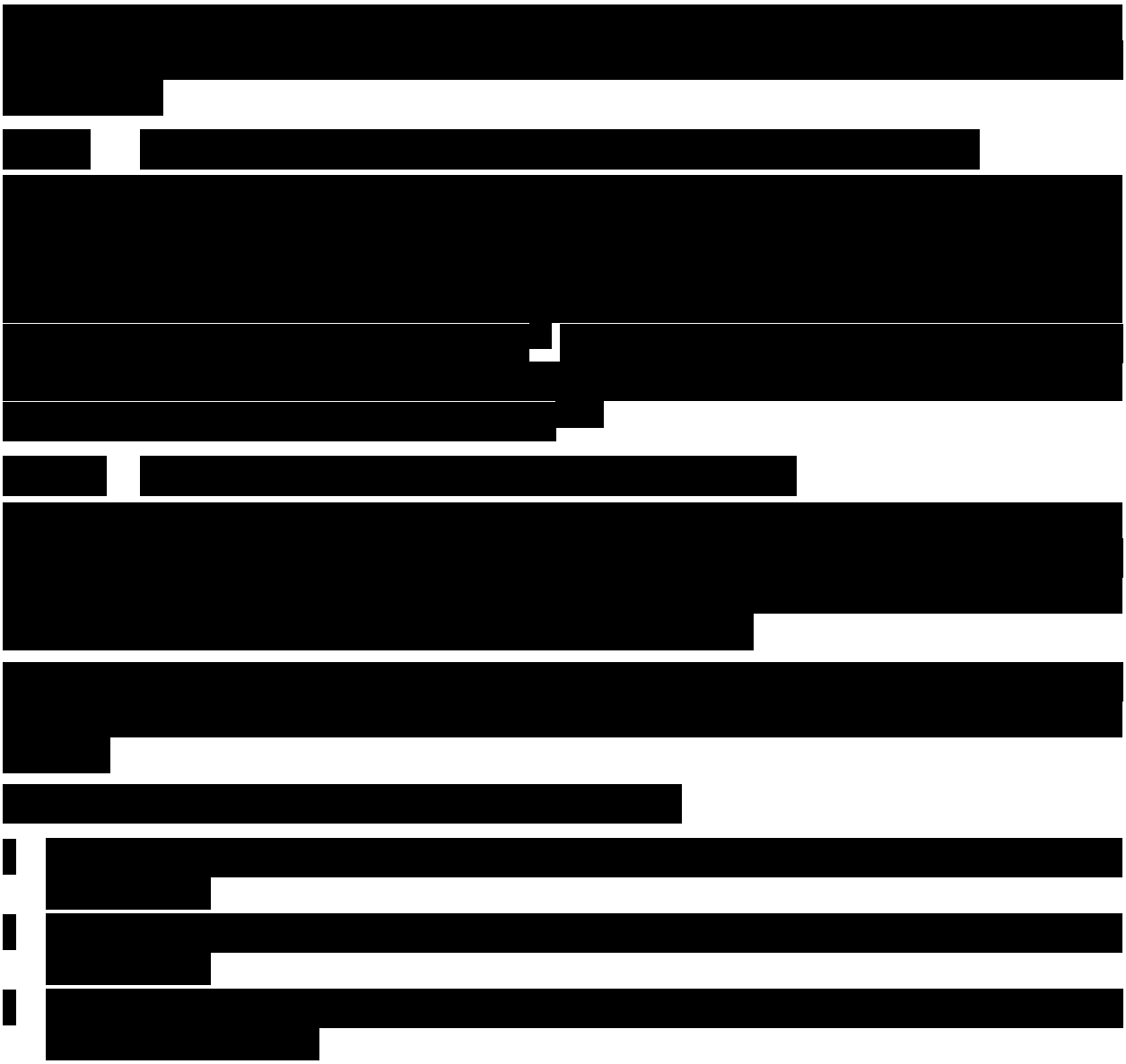


1.2 Research Hypothesis

Treatment with nivolumab will extend disease-free survival, compared with placebo, as adjuvant therapy in all randomized patients and in patients with PD-L1 expressing tumors (membranous staining in ≥ 1%) who are at high risk of recurrence after undergoing radical resection of IUC.

1.3 Objectives

1.3.1 Co-Primary Objectives

- To compare the DFS for nivolumab versus placebo in subjects with tumors expressing PD-L1 (≥ 1% membranous staining in tumor cells) and all randomized subjects

1.3.2 Secondary Objectives

- To compare the overall survival (OS) for nivolumab versus placebo in subjects with tumors expressing PD-L1 (≥ 1% membranous staining in tumor cells) and all randomized subjects
- To evaluate non-urothelial tract recurrence free survival (NUTRFS) in each randomized treatment group (nivolumab versus placebo) in subjects with tumors expressing PD-L1 (≥ 1% membranous staining in tumor cells) and all randomized subjects
- To evaluate disease specific survival (DSS) in each randomized treatment group (nivolumab versus placebo) in subjects with tumors expressing PD-L1 (≥ 1% membranous staining in tumor cells) and all randomized subjects

[redacted]

[redacted]

2 ETHICAL CONSIDERATIONS

2.1 Good Clinical Practice

This study will be conducted in accordance with Good Clinical Practice (GCP), as defined by the International Conference on Harmonization (ICH) and in accordance with the ethical principles underlying European Union Directive 2001/20/EC and the United States Code of Federal Regulations, Title 21, Part 50 (21CFR50).

The study will be conducted in compliance with the protocol. The protocol and any amendments and the subject informed consent will receive Institutional Review Board/Independent Ethics Committee (IRB/IEC) approval/favorable opinion prior to initiation of the study.

All potential serious breaches must be reported to BMS immediately. A serious breach is a breach of the conditions and principles of GCP in connection with the study or the protocol, which is likely to affect, to a significant degree, the safety or physical or mental integrity of the subjects of the study or the scientific value of the study.

Personnel involved in conducting this study will be qualified by education, training, and experience to perform their respective tasks.

This study will not use the services of study personnel where sanctions have been invoked or where there has been scientific misconduct or fraud (eg, loss of medical licensure, debarment).

2.2 Institutional Review Board/Independent Ethics Committee

Before study initiation, the investigator must have written and dated approval/favorable opinion from the IRB/IEC for the protocol, consent form, subject recruitment materials (eg, advertisements), and any other written information to be provided to subjects. The investigator or BMS should also provide the IRB/IEC with a copy of the Investigator Brochure or product labeling information to be provided to subjects and any updates.

The investigator or BMS should provide the IRB/IEC with reports, updates and other information (eg, expedited safety reports, amendments, and administrative letters) according to regulatory requirements or institution procedures.

2.3 Informed Consent

Investigators must ensure that subjects are clearly and fully informed about the purpose, potential risks, and other critical issues regarding clinical studies in which they volunteer to participate.

In situations where consent cannot be given to subjects, their legally acceptable representatives (as per country guidelines) are clearly and fully informed about the purpose, potential risks, and other critical issues regarding clinical studies in which the subject volunteers to participate.

BMS will provide the investigator with an appropriate (ie, Global or Local) sample informed consent form which will include all elements required by ICH, GCP and applicable regulatory requirements. The sample informed consent form will adhere to the ethical principles that have their origin in the Declaration of Helsinki.

Investigators must:

1) Provide a copy of the consent form and written information about the study in the language in which the subject is most proficient prior to clinical study participation. The language must be non-technical and easily understood.
2) Allow time necessary for subject or subject's legally acceptable representative to inquire about the details of the study.
3) Obtain an informed consent signed and personally dated by the subject or the subject's legally acceptable representative and by the person who conducted the informed consent discussion.
4) Obtain the IRB/IEC's written approval/favorable opinion of the written informed consent form and any other information to be provided to the subjects, prior to the beginning of the study, and after any revisions are completed for new information.
5) If informed consent is initially given by a subject's legally acceptable representative or legal guardian, and the subject subsequently becomes capable of making and communicating his or her informed consent during the study, consent must additionally be obtained from the subject.
6) Revise the informed consent whenever important new information becomes available that is relevant to the subject's consent. The investigator, or a person designated by the investigator, should fully inform the subject or the subject's legally acceptable representative or legal guardian, of all pertinent aspects of the study and of any new information relevant to the subject's willingness to continue participation in the study. This communication should be documented.

The confidentiality of records that could identify subjects must be protected, respecting the privacy and confidentiality rules applicable to regulatory requirements, the subjects' signed informed consent form (ICF) and, in the US, the subjects' signed Health Information Portability and Accountability Act (HIPAA) Authorization.

The consent form must also include a statement that BMS and regulatory authorities have direct access to subject records.

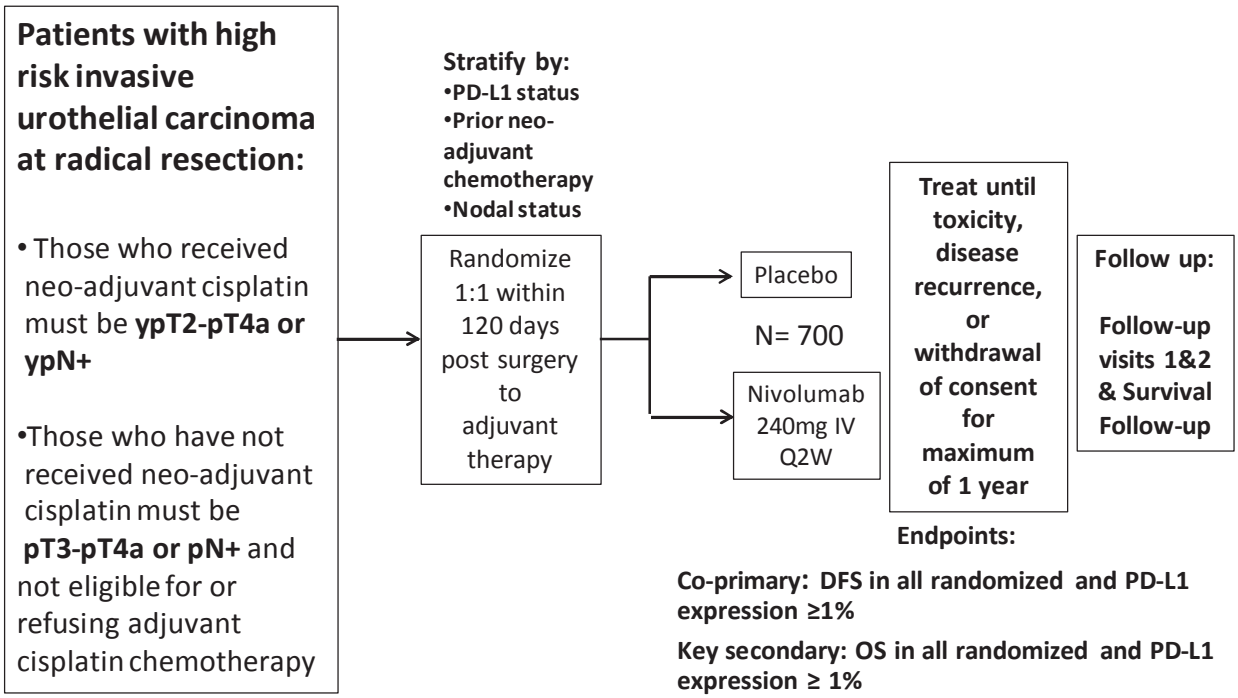
The rights, safety, and well-being of the study subjects are the most important considerations and should prevail over interests of science and society.

3 INVESTIGATIONAL PLAN

3.1 Study Design and Duration

The study design schematic is presented in Figure 3.1-1.

Figure 3.1-1: Study Design Schematic



***Note that Per Revised Protocol 04, there is no longer a cap on the number of subjects with PD-L1 expression <1%.**

This is a phase 3, randomized, double-blind, multicenter trial of adjuvant nivolumab versus placebo in adult male or female subjects who have undergone radical resection of IUC originating in the bladder or upper urinary tract (renal pelvis or ureter) and are at high risk of recurrence:

- Subjects who received neo-adjuvant cisplatin chemotherapy: ypT2-pT4a or ypN+
- Subjects who have not received neo-adjuvant cisplatin chemotherapy: pT3-pT4a or pN+ and are not eligible for or refusing adjuvant cisplatin chemotherapy

Approximately 700 subjects will be randomized in a blinded fashion 1:1 to nivolumab versus placebo within 120 days of radical resection and stratified by pathologic nodal status (N+ vs. N0/x with < 10 nodes removed vs. N0 with ≥ 10 nodes removed), tumor PD-L1 expression (≥ 1%, < 1%/indeterminate), and use of cisplatin neo-adjuvant chemotherapy. Treatment, in the absence of prohibitive toxicities, disease recurrence/progression, or withdrawal of consent will be continued for a maximum of 1 year. The co-primary endpoint is DFS in subjects with tumors expressing PD-L1 at ≥ 1% (2.5% alpha) and in all randomized subjects (2.5% alpha). The overall sample size is set up to allow a clinically meaningful effect to be statistically significant at alpha level of 2.5% (two-sided) in the all randomized group. Even weighting of the alpha distribution between DFS assessment in all randomized (N = 700) and PD-L1 expressers (~ 42% of the all randomized population) reflects an assumption of enrichment of nivolumab efficacy in the PD-L1 expressers. **At the time of the original study design, the anticipated prevalence of**

PD-L1 + was 46%, and the PD-L1-ve population in the study was capped at 54%. During the execution of the study the PD-L1+ rate was ≈42%, for this reason in revised protocol 04 the cap was removed to make the study sample representative of the overall patient population. Hence, it is anticipated that the final population will include approximately 42% of patients who are PD-L1+. The number of randomized subjects with upper tract urothelial cancers (UTUC) will be capped at approximately 20% (140 subjects) of total global enrollment. Once approximately 140 subjects with UTUC are randomized, only subjects with bladder cancer will be enrolled. Following discontinuation of study therapy, subjects will be followed for survival and those that have not had a non-urothelial tract recurrence will be followed for recurrence.

3.1.1 Study Phases

This study will consist of three phases; screening, treatment and follow-up.

Screening Phase:

- Begins by establishing the subject's initial eligibility and signing of the ICF. All efforts should be made to complete screening within 28 days (+/- 3 days) of signing the ICF.
- Subject is enrolled using the Interactive Voice Response System (IVRS).
- Tumor tissue from the most recently resected site of disease (preferable) or from the transurethral resection that yielded the initial muscle invasive diagnosis must be provided for biomarker analyses (block or minimum of 10 unstained slides, obtained from core biopsy, punch biopsy, excisional biopsy or surgical specimen). In order to be randomized, a subject must have a PD-L1 expression level classification (≥ 1%, < 1%, indeterminate) as determined by the central lab. If insufficient tumor tissue content is provided for analysis (eg, unevaluable), acquisition of additional archived tumor tissue from the most recent resection is required. Allow approximately 10 business days from date of shipping prior to randomization for tissue to be received and processed. If PD-L1 result has not been logged into IVRS by the central laboratory randomization will not be allowable through IVRS. Refer to the Lab Manual for more detail.
- Subject is assessed for complete study eligibility within 28 days (+/-3 days) prior to randomization as specified in Table 5.1-1. The subject is eligible is he/she meets all eligibility criteria within 28 days (+/-3 days) prior to randomization even if informed consent was signed outside of 28 days prior to randomization. Of note, screening cystoscopy in patients who have an intact bladder should occur within 60 days prior to randomization.

Baseline disease or tumor imaging assessments should be performed within approximately 28 days prior to randomization (according to Table 5.1-1)

- The screening phase either ends with confirmation of full eligibility and randomization for the subject, or with the confirmation that the subject is a screen failure.
- This study permits the re-enrollment of a subject that has discontinued the study as a pre-treatment failure prior to randomization. If re-enrolled, the subject must be re-consented. A new subject identification number will be assigned by IVRS at the time of re-enrollment.

Treatment Phase:

- The treatment phase begins with the treatment assignment call to the IVRS. Unblinded site personnel will place the call to IVRS to receive the subject's treatment assignment.
- Administration of nivolumab or placebo is to begin within 3 business days of randomization.

Table 3.1.1-1: Treatment Schedule

Drug	Dose	Frequency of administration	Route of administration	Duration
Nivolumab (or placebo)	240 mg	every 2 weeks	Intravenous (IV) infusion	Until toxicity, disease recurrence or discontinuation from study for maximum of 1 year

- Women of child bearing potential (WOCBP) must have a pregnancy test performed within 24 hours prior to first dose, and then every 4 weeks (+ or – 1 week) regardless of the dosing schedule.
- On study vital sign assessments should be performed within 72 hours prior to the first dose and then prior to dosing. Refer to Table 5.1-2.
- During treatment laboratory tests should be drawn within 72 hours prior to dosing through Week 23 and every alternate dose thereafter according to the schedules in Table 5.1-2.

[redacted]

- Treated subjects will be evaluated for recurrence every 12 weeks (± 1 week).
- Treatment phase ends when the subject is discontinued from study therapy or after a maximum of 1 year of treatment. Please refer to Sections 3.5 and 4.5.5 for a complete list of possible reasons for discontinuation.

Follow-up Phase:

- Follow up begins after 1 year of treatment or when the decision is made to discontinue subject from study therapy (eg, due to toxicity or recurrence).
- Subjects who enter the follow-up period without non-urothelial tract recurrence will have surveillance imaging as below:
  - Non-cystoscopy tumor imaging assessments will occur every 12 weeks from the date of first dose to Week 96 (i.e. Week 12, 24, 36, 48, 60, 72, 84, 96; +/- 1 week), then every

16 weeks from Week 96 to Week 160 (i.e. Week 112, 128, 144, 160; +/- 2 weeks), then every 24 weeks until non-urothelial tract recurrence or treatment is discontinued (whichever occurs later) for a maximum of 5 years (i.e. Week 184, 208, 232, 256; +/- 4 weeks).

– Non-cystoscopy tumor imaging assessments: CT of chest, and CT or MRI of abdomen, pelvis, upper urinary tract, and all known sites of disease. Use same imaging method as was used at screening/baseline.

– Cystoscopy in subjects with upper GU primaries who still have bladder intact will occur in addition to other tumor imaging assessments every 12 weeks from the date of first dose to Week 48 (i.e. Week 12, 24, 36, 48 +/- 1 week), then every 24 weeks from Week 48 to Week 96 (i.e. Week 72, 96; +/- 2 weeks), then every 48 weeks until non-urothelial tract recurrence or treatment is discontinued (whichever occurs later) for a maximum of 5 years (i.e. Week 144, 192, 240; +/- 4 weeks).

[redacted]

- Subjects will have two follow-up visits (FU1 and FU2) for safety within approximately 100 days from the last dose of study therapy, according to Table 5.1-3. Beyond this time period, subjects will be followed for survival and ongoing drug related AEs until these events have resolved, returned to baseline or are deemed irreversible.
- After discontinuation of study therapy (nivolumab/placebo) and completion of follow-up visits FU1 and FU2, subjects will be followed every 3 months (+/- 7 days) for survival and second progression until death, lost to follow-up, withdrawal of study consent or end of study.

Assuming an average accrual rate of 16 subjects per month, the accrual will take approximately 40 months. The total duration of the study from start of randomization to final analysis of DFS is expected to be 53 months (40 months of accrual + 13 months of follow-up) (Table 8.1-1). Additional survival follow-up may continue for up to 5 years from the primary analysis of DFS. The study will end once survival follow-up has concluded.

3.1.2 Review of Safety

The subjects' safety will be monitored on an ongoing basis as described fully in Section 5.3. In addition, a BMS medical safety team (MST) routinely reviews safety signals across the entire nivolumab program. An independent Data Monitoring Committee (DMC) will provide safety reviews every six months or as defined in the DMC Charter. Decisions regarding safety will be made by the sponsor in conjunction with feedback from the investigators and the DMC (See Section 7).

3.1.3 Dose reductions

Dose reductions are not permitted for any reason. Dose delays for the management of study treatment related adverse events are described in Section 4.5.3.

3.2 Post Study Access to Therapy

At the end of the study, BMS will not continue to provide BMS supplied study drug to subjects/investigators unless BMS chooses to extend the study. The study is designed to have a maximum treatment duration of 1 year and at the end of the study no subjects are expected to be on treatment. The investigator should ensure that the subject receives appropriate standard of care to treat the condition under study.

3.3 Study Population

For entry into the study, the following criteria must be met.

3.3.1 Inclusion Criteria

1) Signed Written Informed Consent
   a) Subjects must have signed and dated an IRB/IEC approved written informed consent form in accordance with regulatory and institutional guidelines. This must be obtained before the performance of any protocol related procedures that are not part of normal subject care.
   b) Subjects must be willing and able to comply with scheduled visits, treatment schedule, laboratory tests, tumor biopsies, and other requirements of the study.
2) Target Population
   a) All subjects must be status post radical surgical resection (R0) for IUC, performed within 120 days prior to randomization. Subjects with carcinoma in situ in surgical margins are not eligible for study entry.
   b) All subjects must have pathologic evidence of urothelial carcinoma (originating in bladder, ureter, or renal pelvis) at high risk of recurrence based on pathologic staging of radical surgery tissue as described in one of the two below scenarios (i or ii):
      i) Subjects who have not received neo-adjuvant cisplatin chemotherapy: pT3-pT4a or pN+ and are not eligible for or refusing adjuvant cisplatin chemotherapy
         (1). Subjects ineligible for adjuvant cisplatin due to any of the following criteria:[50]
            a. Creatinine Clearance (using the Cockcroft-Gault formula): < 60 mL/min
            b. Common Terminology Criteria for Adverse Events (CTCAE) version 4, grade 2 or above audiometric hearing loss
            c. CTCAE version 4, grade 2 peripheral neuropathy
            d. Eastern Cooperative Oncology Group Performance Scale (ECOG PS) 2
            e. NYHA Class III or IV Heart Failure
         (2). Subjects that are eligible for cisplatin may be candidates if they refuse available adjuvant chemotherapy, despite being informed by the investigator about the treatment options. The subject's refusal must be thoroughly documented.
      ii) Subjects who received neo-adjuvant cisplatin chemotherapy: ypT2-pT4a or ypN+
   c) Dominant component of histology needs to be urothelial carcinoma or transitional cell carcinoma. Foci of varied histologies (eg, minor variants) are accepted.
   d) All subjects must have disease-free status defined as no clinical or radiographic evidence of recurrence of disease documented by a complete physical examination and imaging

studies within 4 weeks prior to randomization. Subjects with equivocal nodes less than 15 mm in short axis not considered by the investigator to represent malignant disease may be eligible if discussed and approved by BMS Medical Monitor. All suspect lesions identified during screening radiographic procedures should be discussed with the Medical Monitor prior to randomization.

i) Imaging studies must include CT of chest and CT or MRI of abdomen, pelvis, and all known sites of resected disease including cystoscopy in subjects with upper GU primaries who still have bladder intact. Brain imaging (MRI except where contraindicated in which CT scan is acceptable) must be completed within 28 days prior to randomization for subjects with clinical suspicion or history of brain/leptomeningeal metastases.

ii) Subjects who are found to have high-risk NMIBC at the time of screening are not eligible for study entry. Patients with low-risk papillary lesions may enter the study if rendered free of disease at cystoscopy. Subjects with intermediate-risk NMIBC may enter the study if intravesical chemotherapy or BCG is not required. Screening cystoscopy may occur within 60 days of randomization and is encouraged to be done prior to other imaging. Any suspect lesions seen on cystoscopy should be biopsied to rule-out the possibility of high-risk lesions.

Low-risk NMIBC is defined as low-grade lesions or papillary urothelial neoplasms of low malignant potential (PUNLMP; WHO/ISUP 2004 grading system), or TaG1 lesions (WHO 1973 grading system) that are less than 3 cm in diameter.

High-risk NMIBC is defined as any T1 lesion, any lesion containing carcinoma in situ (CIS) either alone or concomitantly with papillary disease (e.g. CIS with Ta/T1 lesions), and any Ta high-grade (TaHG; WHO/ISUP 2004 grading system) or TaG3 (WHO 1973 grading system) lesion.

Intermediate-risk NMIBC is defined as lesions not meeting the criteria of high-risk or low-risk.

[redacted]

f) Life expectancy ≥ 6 months

[redacted]

h) Prior surgery that required general anesthesia must be completed at least 4 weeks before study drug administration. Surgery requiring local/epidural anesthesia must be completed at least 72 hours before study drug administration. Trans-urethral resection of bladder tumor (TURBT) must be completed 14 days before randomization.

j) Re-enrollment: This study permits the re-enrollment of a subject who has discontinued the study as a pre-treatment failure prior to randomization. If re-enrolled, the subject must be re-consented. A new subject identification number will be assigned by IVRS at the time of re-enrollment.

3) Age and Reproductive Status

a) Men and women, ages ≥ 18 years of age

b) WOCBP must have a negative serum or urine pregnancy test (minimum sensitivity 25 IU/L or equivalent units of beta-human chorionic gonadotropin [HCG]) within 24 hours prior to the start of study drug.

c) Women must not be breastfeeding

d) WOCBP must agree to follow instructions for method(s) of contraception from the time of enrollment for the duration of treatment with study drug(s) plus 5 months post-treatment completion.

e) Men who are sexually active with WOCBP must agree to follow instructions for method(s) of contraception for the duration of treatment with study drug(s) plus 7 months post-treatment completion.

f) Azoospermic males and WOCBP who are continuously not heterosexually active are exempt from contraceptive requirements. However, WOCBP must still undergo pregnancy testing as described in these sections.

Investigators shall counsel WOCBP and male subjects who are sexually active with WOCBP on the importance of pregnancy prevention and the implications of an unexpected pregnancy. Investigators shall advise WOCBP and male subjects who are sexually active with WOCBP on the use of highly effective methods of contraception. Highly effective methods of contraception have a failure rate of < 1% when used consistently and correctly.

At a minimum, subjects must agree to the use of one method of highly effective contraception, (See Appendix 3.)

3.3.2 Exclusion Criteria

1) Target Disease Exceptions
   a) Partial cystectomy in the setting of bladder cancer primary tumor or partial nephrectomy in the setting of renal pelvis primary tumor.
   b) Adjuvant systemic or radiation therapy for urothelial or prostatic carcinoma following radical surgical resection of urothelial carcinoma.
2) Medical History and Concurrent Diseases.
   a) Any serious or uncontrolled medical disorder that, in the opinion of the investigator, may increase the risk associated with study participation or study drug administration, impair the ability of the subject to receive protocol therapy, or interfere with the interpretation of study results.
   b) Prior malignancy active within the previous 3 years except for locally curable cancers that have been apparently cured, such as basal or squamous cell skin cancer, prostate cancer with evidence of undetectable Prostate Specific Antigen (PSA) or carcinoma in situ of the prostate, cervix or breast. Patients with known history of recent metastatic urothelial carcinoma will be excluded.
   c) Subjects with active, known or suspected autoimmune disease. Subjects with vitiligo, type I diabetes mellitus, residual hypothyroidism due to autoimmune condition only requiring hormone replacement, psoriasis not requiring systemic treatment, or conditions not expected to recur in the absence of an external trigger are permitted to enroll.
   d) Subjects with a condition requiring systemic treatment with either corticosteroids (> 10 mg daily prednisone equivalents) or other immunosuppressive medications within 14 days of study drug administration. Inhaled or topical steroids and adrenal replacement doses > 10 mg daily prednisone equivalents are permitted in the absence of active autoimmune disease.
   e) Subjects with history of life-threatening toxicity related to prior immune therapy (eg. anti-CTLA-4 or anti-PD-1/PD-L1 treatment or any other antibody or drug specifically targeting T-cell co-stimulation or immune checkpoint pathways) except those that are unlikely to re-occur with standard countermeasures (eg. hormone replacement after adrenal crisis).
   f) All toxicities attributed to prior anti-cancer therapy other than nephropathy, neuropathy, hearing loss, alopecia and fatigue must have resolved to Grade 1 (NCI CTCAE version 4) or baseline before administration of study drug. Subjects with toxicities attributed to prior anti-cancer therapy which are not expected to resolve and result in long lasting sequelae, such as neuropathy after platinum based therapy, are permitted to enroll. See Inclusion

criterion 2) i) (5) for renal function eligibility. Neuropathy must have resolved to Grade 2 (NCI CTCAE version 4).

g) Treatment with any chemotherapy radiation therapy, biologics for cancer, intravesical therapy, or investigational therapy within 28 days of first administration of study treatment

h) Subjects who have received a live/attenuated vaccine within 30 days of randomization (eg, varicella, zoster, yellow fever, rotavirus, oral polio and measles, mumps, rubella [MMR]).

i) Treatment with botanical preparations (eg herbal supplements or traditional Chinese medicines) intended for general health support or to treat the disease under study within 2 weeks prior to randomization/treatment. Refer to Section 3.4.1 for prohibited therapies.

3) Physical and Laboratory Test Findings
   a) Positive test for hepatitis B virus surface antigen (HBV sAg) or hepatitis C virus (ribonucleic acid or HCV antibody) indicating acute or chronic infection prior to randomization
   b) Known history of testing positive for human immunodeficiency virus (HIV) or known acquired immunodeficiency syndrome (AIDS).
4) Allergies and Adverse Drug Reaction
   a) History of allergy to study drug components.
   b) History of severe hypersensitivity reaction to any monoclonal antibody.
5) Sex and Reproductive Status
   a) WOCBP who are pregnant or breastfeeding
   b) Women with a positive pregnancy test at enrollment or prior to administration of study medication
6) Other Exclusion Criteria
   a) Prisoners or subjects who are involuntarily incarcerated
   b) Subjects who are compulsorily detained for treatment of either a psychiatric or physical (eg, infectious disease) illness.
   c) Psychological, familial, sociological, or geographical conditions that potentially hamper compliance with the study protocol and follow-up schedule; those conditions should be discussed with the subject before registration in the trial.

Eligibility criteria for this study have been carefully considered to ensure the safety of the study subjects and that the results of the study can be used. It is imperative that subjects fully meet all eligibility criteria.

3.3.3 Women of Childbearing Potential

A WOCBP is defined as any female who has experienced menarche and who has not undergone surgical sterilization (hysterectomy or bilateral oophorectomy) and is not postmenopausal. Menopause is defined as 12 months of amenorrhea in a woman over age 45 years in the absence

of other biological or physiological causes. In addition, females under the age of 55 years must have a serum follicle stimulating hormone, (FSH) level > 40mIU/mL to confirm menopause.

*Females treated with hormone replacement therapy, (HRT) are likely to have artificially suppressed FSH levels and may require a washout period in order to obtain a physiologic FSH level. The duration of the washout period is a function of the type of HRT used. The duration of the washout period below are suggested guidelines and the investigators should use their judgment in checking serum FSH levels. If the serum FSH level is > 40 mIU/ml at any time during the washout period, the woman can be considered postmenopausal:

- 1 week minimum for vaginal hormonal products (rings, creams, gels)
- 4 week minimum for transdermal products
- 8 week minimum for oral products

Other parenteral products may require washout periods as long as 6 months.

[redacted]

[redacted]

3.4.3 Permitted Therapy

Subjects are permitted the use of topical, ocular, intra-articular, intranasal and inhalational corticosteroids (with minimal systemic absorption). Physiologic replacement doses of systemic corticosteroids are permitted even if > 10 mg daily prednisone (or equivalent). A brief course of corticosteroids (3 weeks) for prophylaxis (eg, for contrast dye allergy) or for treatment of non-autoimmune conditions (eg, delayed-type hypersensitivity reaction caused by a contact allergen) is permitted.

Intravitreal injections of vascular endothelial growth (VEGF) inhibitors are permitted if used according to the approved ocular indication, such as macular degeneration.

3.5 Discontinuation of Subjects following any Treatment with Study Drug

Subjects MUST discontinue investigational product (and non-investigational product at the discretion of the investigator) for any of the following reasons:

- Subject's request to stop study treatment
- Recurrence (local, regional or distant)
- Any clinical AE, laboratory abnormality or intercurrent illness which, in the opinion of the investigator, indicates that continued participation in the study is not in the best interest of the subject
- Termination of the study by BMS
- Loss of ability to freely provide consent through imprisonment or involuntarily incarceration for treatment of either a psychiatric or physical (eg, infectious disease) illness
- Additional protocol specified reasons for discontinuation (see Section 4.5.5)

In the case of pregnancy, the investigator must immediately notify the BMS Medical Monitor/designee of this event. In most cases, the study therapy will be permanently discontinued in an appropriate manner. If the investigator determines a possible favorable benefit/risk ratio that warrants continuation of the study drug, a discussion between the investigator and the BMS Medical Monitor/designee must occur.

All subjects who discontinue study therapy should comply with protocol specified follow-up procedures as outlined in Section 5. The only exception to this requirement is when a subject withdraws consent for all study procedures including post-treatment study follow-up or loses the ability to consent freely (ie, is imprisoned or involuntarily incarcerated for the treatment of either a psychiatric or physical illness).

If study drug is discontinued prior to the subject's completion of the study, the reason for the discontinuation must be documented in the subject's medical records and entered on the appropriate case report form (CRF) page.

Subjects must be followed for at least 100 days after the last dose of study therapy. Follow-up visit #1 (FU1) occurs approximately 35 days (+/- 7 days) after last dose or coinciding with the date of discontinuation (+/- 7 days) if the date of discontinuation is greater than 35 days after the last dose. Follow up visit #2 (FU2) occurs approximately 80 days (+/- 7 days) after FU1. Survival visits are every 3 months from FU2 until the end of the study (5 years from the primary analysis of DFS) and may be conducted during a clinic visit or via the phone. The co-primary endpoint of this study is DFS in all randomized and in PD-L1 expressers (≥ 1% membranous tumor staining) and a key secondary endpoint is OS so tracking and reporting the subject's status in the follow up setting according to the protocol guidelines for disease recurrence and survival are critical to the final study analysis. The importance of follow up should be clearly communicated to study subjects.

3.6 Post Study Drug Study Follow up

In this study, DFS and OS are key endpoints. Post study follow-up is of critical importance and is essential to preserving subject safety and the integrity of the study. Subjects who discontinue study drug must continue to be followed for collection of outcome and/or survival follow-up data as required and in line with Section 5 until death or the conclusion of the study.

BMS may request that survival data be collected on all randomized subjects outside of the protocol defined window (Table 5.1-3). At the time of this request, each subject will be contacted to determine their survival status unless the subject has withdrawn consent for all contact.

3.6.1 Withdrawal of Consent

Subjects who request to discontinue study drug will remain in the study and must continue to be followed for protocol specified follow-up procedures. The only exception to this is when a subject specifically withdraws consent for any further contact with him/her or persons previously authorized by subject to provide this information. Subjects should notify the investigator of the decision to withdraw consent from future follow-up **in writing**, whenever possible. The withdrawal of consent should be explained in detail in the medical records by the investigator, as to whether the withdrawal is from further treatment with study drug only or also from study procedures and/or post treatment study follow-up, and entered on the appropriate CRF page. In the event that vital status (whether the subject is alive or dead) is being measured, publicly available information should be used to determine vital status only as appropriately directed in accordance with local law.

3.6.2 Lost to Follow-Up

All reasonable efforts must be made to locate subjects to determine and report their ongoing status. This includes follow-up with persons authorized by the subject as noted above. Lost to follow-up is defined by the inability to reach the subject after a minimum of three documented phone calls, faxes, or emails as well as lack of response by subject to one registered mail letter.

All attempts should be documented in the subject's medical records. If it is determined that the subject has died, the site will use permissible local methods to obtain the date and cause of death.

If investigator's use of third-party representative to assist in the follow-up portion of the study has been included in the subject's informed consent, then the investigator may use a Sponsor-retained third-party representative to assist site staff with obtaining subject's contact information or other public vital status data necessary to complete the follow-up portion of the study. The site staff and representative will consult publicly available sources, such as public health registries and databases, in order to obtain updated contact information. If after all attempts, the subject remains lost to follow-up, then the last known alive date as determined by the investigator should be reported and documented in the subject's medical records.

4 STUDY DRUG

Study drug includes both Investigational [Medicinal] Product (IP/IMP) and Non-investigational [Medicinal] Product (Non-IP/Non-IMP) and can consist of the following:

- All products, active or placebo, being tested or used as a comparator in a clinical trial.
- Study required premedication, and
- Other drugs administered as part of the study that are critical to claims of efficacy (eg, background therapy, rescue medications)

Table 4-1: Study Drugs for CA209274

Product Description / Class and Dosage Form	Potency	IP/Non-IMP	Blinded or Open Label	Packaging/ Appearance	Storage Conditions (per label)
BMS-936558-01 (Nivolumab) Solution for Injection[a]	100 mg (10 mg/mL)	IP	Open-Label	10 mL per vial (10 or 5 vials/carton)	Store at 2° - 8 °C. Protect from light and freezing.
0.9% Sodium Chloride for Injection Solution (used as placebo for nivolumab)[b]	N/A	IP	Open-Label	IV bag/container (sourced as local commercial product)	Store at 2° - 8 °C. Protect from light and freezing.
5% Dextrose for Injection Solution (used as placebo for nivolumab)[b]	N/A	IP	Open-Label	IV bag/container (sourced as local commercial product)	Store at 2° - 8 °C. Protect from light and freezing.

[a] The term "open label" refers to the medication as it is upon receipt at the pharmacy. The trial will be conducted in a double-blinded fashion.

[b] Diluents used for nivolumab and to prepare matching placebo. These will be sourced by the investigative sites if permitted by local regulations.

Pre-medications or medications used to treat infusion-related reactions should be sourced by the investigative sites if available and permitted by local regulations.

4.1 Investigational Product

An investigational product, also known as investigational medicinal product in some regions, is defined a pharmaceutical form of an active substance or placebo being tested or used as a reference in a clinical study, including products already with a marketing authorization but used or assembled (formulated or packaged) differently than the authorized form, or used for an unauthorized indication, or when used to gain further information about the authorized form.

The investigational product should be stored in a secure area according to 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.

In this protocol, investigational products are: nivolumab and placebo for nivolumab (0.9% sodium chloride for injection or 5% dextrose for injection).

4.2 Non-investigational Product

Other medications used as support or escape medication for preventative, diagnostic, or therapeutic reasons, as components of the standard of care for a given diagnosis, may be considered as non-investigational products.

In this protocol, non-investigational product(s) is/are: medications used to treat nivolumab infusion-related reactions (eg, steroids, anti-emetics); these non-investigational products should be sourced by the investigator sites if available and permitted by local regulations.

4.3 Storage and Dispensing

The product storage manager should ensure that the study drug is stored in accordance with the environmental conditions (temperature, light, and humidity) as determined by BMS. If concerns regarding the quality or appearance of the study drug arise, the study drug should not be dispensed and contact BMS immediately.

Study drug not supplied by BMS will be stored in accordance with the package insert.

Investigational product documentation (whether supplied by BMS or not) must be maintained that includes all processes required to ensure drug is accurately administered. This includes documentation of drug storage, administration and, as applicable, storage temperatures, reconstitution, and use of required processes (eg, required diluents, administration sets).

Infusion-related supplies (eg, IV bags, in-line filters, diluents) will not be supplied by the sponsor and should be purchased locally if permitted by local regulations.

For nivolumab, please refer to the current version of the Investigator Brochure and/or pharmacy reference sheets for complete storage, handling, dispensing, and infusion information. For diluents, please refer to the package insert, summary of product characteristics, or equivalent documentation.

Once diluents are prepared/assigned as placebo, they should be stored/handled/dispensed/infused in an identical fashion as nivolumab in order to maintain the blind.

The unblinded pharmacist will obtain treatment assignment by IVRS and prepare blinded drug.

At the end of the infusion, flush the line with a sufficient quantity of diluent.

4.4 Method of Assigning Subject Identification

After the subject's initial eligibility is established and informed consent has been obtained, the subject must be enrolled into the study by calling an IVRS to obtain the subject number. Every subject that signs the informed consent form must be assigned a subject number in IVRS. Specific instructions for using IVRS will be provided to the investigational site in a separate document. The investigator or designee will register the subject for enrollment by following the enrollment procedures established by BMS. The following information is required for enrollment:

- Date that informed consent was obtained
- Date of birth
- Gender at birth.

Once enrolled in IVRS, subjects that have met all eligibility criteria (including the required tumor tissue received/processed and PD-L1 expression result logged into the IVRS by the central laboratory as well as the pathology report being approved by the investigator) will be ready to be randomized through the IVRS. The randomization call to address eligibility questions will be performed by the blinded site staff. Once the subject is randomized, the unblinded pharmacy site staff will make a separate call to IVRS to obtain the treatment assignment. The following information is required for subject randomization:

- Subject number
- Date of birth
- PD-L1 evaluable status (Note that the result of PD-L1 expression ≥ 1%, PD-L1 expression < 1% or indeterminate is entered by the central laboratory vendor into the IVRS system and both the site and the BMS clinical study team members remain blinded to the result)
- Receipt of neo-adjuvant cisplatin based chemotherapy for IUC (Yes/No)
- Pathologic status of disease in lymph nodes (N+ or N0/x with < 10 nodes removed or N0 with ≥ 10 nodes removed)

Subjects meeting all eligibility criteria will be randomized in a 1:1 ratio to Arm A (nivolumab) or Arm B (placebo) stratified by the following factors:

- PD-L1 expression level (≥ 1% vs. < 1%/indeterminate)
- Receipt of neo-adjuvant cisplatin based chemotherapy for IUC (Yes/No)
- Pathologic status of disease in lymph nodes (N+ vs. N0/x with < 10 nodes removed vs. N0 with ≥ 10 nodes removed)

The exact procedures for using the IVRS will be detailed in the IVRS manual.

4.5 Selection and Timing of Dose for Each Subject

Table 4.5-1: Nivolumab (or placebo) dosing

Drug	Dose	Frequency of administration	Route of administration	Duration
Nivolumab (or placebo)	Flat dose of 240 mg	every 2 weeks	Intravenous (IV) infusion	Until recurrence or discontinuation from study for a maximum of 1 year

Subjects will receive treatment with nivolumab or placebo as a 30 minute IV infusion on Day 1 of a treatment cycle every 2 weeks (14 days), for a maximum of 1 year or until recurrence, or unacceptable toxicity, withdrawal of consent, or the study ends, whichever occurs first. The first dose must be administered within 3 business days following randomization. There are no pre-medications recommended on the first cycle. If an acute infusion reaction is noted, subjects should be managed according to Section 4.5.6. At the end of the infusion, flush the line with a sufficient quantity of dextrose or normal saline. Refer to Pharmacy Information sheets for more detail.

Dosing modifications:

There will be no dose modifications (dose escalations or reductions) allowed for the management of toxicities of individual subjects.

Dosing window:

Subjects may be dosed no less than 12 days between doses and no more than 3 days after the scheduled dosing date. If a dose is given after the 3 day window it is considered a dose delay. A maximum delay of 42 days between doses is allowed.

Placebo arm:

The Sponsor, subjects, investigator and site staff will be blinded to the study drug administered. Each investigative site must assign an unblinded pharmacist/designee. Commercially available normal saline or dextrose will be used for subjects randomized to placebo. No active drug will be mixed with the normal saline or dextrose. See the pharmacy information sheets and current IB for additional details.

4.5.1 Antiemetic Premedications

Antiemetic premedications should not be routinely administered prior to dosing of drugs. See Section 4.5.6 for premedication recommendations following a nivolumab related infusion reaction.

4.5.2 Dose Delay Criteria

Dose delay criteria apply for all drug-related adverse events. Treatment delays up to 6 weeks (42 days) from the last dose are allowable.

Nivolumab (or placebo) administration should be delayed for the following:

- Any Grade ≥ 2 non-skin, drug-related adverse event, with the following exceptions:
  - Grade 2 drug-related fatigue or laboratory abnormalities do not require a treatment delay
- Any Grade 3 skin, drug-related adverse event
- Any Grade 3 drug-related laboratory abnormality, with the following exceptions for asymptomatic amylase or lipase, AST, ALT, or total bilirubin:
  - Grade 3 lymphopenia does not require dose delay
  - Grade 3 amylase or lipase abnormalities that are not associated with symptoms or clinical manifestations of pancreatitis do not require a dose delay. It is recommended to consult with the BMS Medical Monitor for Grade 3 amylase or lipase abnormalities.
  - 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 adverse event, 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 (or placebo) should be re-evaluated weekly or more frequently if clinically indicated and resume nivolumab (or placebo) dosing when re-treatment criteria are met.

Note: per BMS standards, the term “interruption” is reserved for interruption of the actual IV infusion during administration. The terms delay and interruption should not be used synonymously when completing the CRF forms.

4.5.2.1 Adverse Event Management Algorithms for Immuno-Oncology Agents

Immuno-oncology (I-O) agents are associated with adverse events that can differ in severity and duration than adverse events caused by other therapeutic classes. Nivolumab is considered an immuno-oncology agent in this protocol. Early recognition and management of adverse events 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 adverse events:

- Gastrointestinal
- Renal
- Pulmonary

- Hepatic
- Endocrinopathies
- Skin
- Neurological
- Myocarditis

In order to standardize the management of adverse events for all subjects, treatment management algorithms recommended for utilization in this study are from the current IB and included in Appendix 1. Adverse event treatment management algorithms included in Appendix 1 might be considered for individual cases.

For subjects expected to require more than 4 weeks of corticosteroids or other immunosuppressants to manage an adverse event, consider recommendations provided in Appendix 1.

4.5.3 Dose Modifications

Dose reductions for the management of toxicities of individual subjects or dose escalations are not permitted. All dose modification rules apply to both arms given the blinded nature of this study.

4.5.4 Criteria to Resume Treatment

All criteria to resume treatment apply to both arms given the blinded nature of this study.

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
- Drug-related endocrinopathies adequately controlled with only physiologic hormone replacement may resume treatment.

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

However, if the treatment is withheld past the window period of the next scheduled timepoint per protocol to ensure adequate recovery from the adverse event or tapering of immunosuppression, the dosing should continue to be withheld until the subsequent scheduled timepoint.

If treatment is delayed > 6 weeks from the last dose, the subject must be permanently discontinued from study therapy, except as specified in Section 4.5.5.

4.5.5 Discontinuation Criteria

All discontinuation criteria apply to both arms given the blinded nature of this study.

Treatment with nivolumab (or placebo) should be permanently discontinued for the following:

- 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, diarrhea, colitis, neurologic toxicity, hypersensitivity reactions, and infusion reactions:
  - Grade 3 drug-related uveitis, pneumonitis, bronchospasm, diarrhea, colitis, neurologic toxicity, 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:
    - 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 > 2x ULN
- Any Grade 4 drug-related adverse event or laboratory abnormality, except for the following events which do not require discontinuation:
  - Grade 4 neutropenia ≤ 7 days
  - Grade 4 lymphopenia or leukopenia
  - Isolated Grade 4 amylase or lipase abnormalities that are not associated with symptoms or clinical manifestations of pancreatitis. It is recommended to consult with the BMS Medical Monitor for Grade 4 amylase or lipase abnormalities.
  - 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
  - For Grade 4 endocrinopathy adverse events such as adrenal insufficiency, ACTH deficiency, hyper- or hypothyroidosis, or glucose intolerance, which resolve or are

adequately controlled with physiologic hormone replacement (steroids, thyroid hormones) or glucose controlling agents, respectively.

- Any dosing delay lasting > 6 weeks from the last dose with the following exceptions:
  - Dosing delays 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 from the last dose, the BMS Medical Monitor must be consulted. Tumor imaging assessments should continue as per protocol even if dosing is interrupted.
  - Dosing delays > 6 weeks from the last dose that occur for non-drug-related reasons may be allowed if approved by the BMS Medical Monitor. Tumor imaging 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 (or placebo) dosing.

Tumor assessments for all subjects should continue until non-urothelial tract recurrence as per protocol even if study drug dosing is discontinued. Tumor assessments, QoL questionnaires collection and biomarker sampling should continue as per protocol even if dosing is omitted.

4.5.6 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, pruritus, arthralgias, hypo- or hypertension, bronchospasm, or other symptoms. All Grade 3 or 4 infusion reactions should be reported within 24 hours to the BMS Medical Monitor and reported as an SAE if criteria are met. Infusion reactions should be graded according to NCI CTCAE (version 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 pruritus within 1 week after treatment), symptomatic treatment may be given (eg, oral antihistamine, or corticosteroids).

4.6 Blinding/Unblinding

The Sponsor, subjects, investigator and site staff will be blinded to the study therapy administered. Each investigative site must assign an unblinded pharmacist/designee, and an unblinded site monitor will be assigned to provide oversight of drug supply and other unblinded study documentation.

Blinding of treatment assignment is critical to the integrity of this clinical study. However, in the event of a medical emergency of pregnancy in an individual subject in which knowledge of the investigational product is critical to the subject's management, the blind for that subject may be broken by the investigator. The subject's safety takes priority over any other considerations in determining if the treatment assignment should be unblinded.

Before breaking the blind of an individual subject's treatment, the investigator should determine that the unblinded information is necessary, ie, that it will alter the subject's immediate management. In many cases, particularly when the emergency is clearly not related to the

investigational product, the problem may be properly managed by assuming that the subject is receiving active product. It is highly desirable that the decision to unblind treatment assignment be discussed with the Medical Monitor, but the investigator always has ultimate authority for the decision to unblind. The actual TASK of unblinding can be delegated by the investigator to a designee assigned the task on the Delegation of Authority. The Principal Investigator or appointed designee should only call in for emergency unblinding AFTER the decision to unblind the subject has been documented.

For this study, the method of unblinding for emergency purposes is through the IVRS. For information on how to unblind for emergency, please consult the IVRS manual.

In cases of accidental unblinding, contact the BMS Medical Monitor and ensure every attempt is made to preserve the blind.

Any request to unblind a subject for non-emergency purposes should be discussed with the BMS Medical Monitor.

Designated staff of BMS Research & Development may be unblinded prior to database lock to facilitate the bioanalytical analysis of pharmacokinetic samples and immunogenicity. A bioanalytical scientist in the Bioanalytical Sciences department of BMS Research & Development (or a designee in the external central bioanalytical laboratory) will be unblinded to the randomized treatment assignments in order to minimize unnecessary bioanalytical analysis of samples.

To further minimize bias, the investigative clinical site staff is blinded to results from PD-L1 analysis.

4.7 Treatment Compliance

Treatment compliance will be monitored by drug accountability as well as the subject's medical record and electronic CRF (eCRF).

4.8 Destruction of Study Drug

For this study, study drugs (those supplied by BMS or sourced by the investigator) such as partially used study drug containers, vials and syringes may be destroyed on site.

Any unused study drugs can only be destroyed after being inspected and reconciled by the responsible Study Monitor unless study drug containers must be immediately destroyed as required for safety, or to meet local regulations (eg, cytotoxics or biologics).

On-site 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 site's 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 the Monitor to review throughout the clinical trial period.

If conditions for destruction cannot be met the responsible Study Monitor will make arrangements for return of study drug.

It is the 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.

4.9 Return of Study Drug

If study drug will not be destroyed upon completion or termination of the study, all unused and/or partially used study drug that was supplied by BMS must be returned to BMS. The return of study drug will be arranged by the responsible Study Monitor.

It is the 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.

5 STUDY ASSESSMENTS AND PROCEDURES

5.1 Flow Chart/Time and Events Schedule

Table 5.1-1: Screening Procedural Outline (CA209274)

Procedure	Screening Visit	Notes
Eligibility Assessments		
Informed Consent	X	IC in screening for protocol participation; Study allows for re-enrollment of a subject that has discontinued the study as a pre-randomization failure. If re-enrolled, the subject must be re-consented and assigned a new subject number from IVRS.
Inclusion/Exclusion Criteria	X	All inclusion/exclusion criteria should be assessed and confirmed prior to randomization.
Medical History	X	Including smoking history
Tumor Tissue Sample	X	Sufficient tumor tissue from the resected site of disease (a block or a minimum of 10 unstained slides) must be available and sent to a central laboratory for biomarker analysis. PD-L1 status will be assessed prior to randomization. See Section 5.6.1
Prior Cancer Therapy	X	All prior therapy should be reported.
[redacted]	X	[redacted]
Safety Assessments		
Physical Examination	X	General physical examination including assessment for hearing loss and peripheral neuropathy as needed within 14 days prior to randomization
Vital Signs	X	Including BP, HR and temperature. Obtain vital signs at the screening visit and within 72 hours prior to first dose.
Physical Measurements	X	Section 5.3. Include Height and weight. Within 14 days prior to randomization
Assessment of Signs and Symptoms	X	Within 14 days prior to randomization
Concomitant Medication Collection	X	Within 14 days prior to randomization

Table 5.1-1: Screening Procedural Outline (CA209274)

Procedure	Screening Visit	Notes
Laboratory Tests	X	CBC w/differential and platelet count, Chemistry panel including: LDH, AST, ALT, ALP, T.Bili, BUN or serum urea level, creatinine, Ca, Mg, Na, K, Cl, Glucose within 14 days prior to randomization Urinalysis/Urine Cytology as clinically indicated within 14 days prior to randomization. Amylase, lipase, albumin, TSH (Reflex to Free T4, Free T3 for abnormal TSH result), Hepatitis B surface antigen (HBV sAg), and hepatitis C antibody (HCV Ab) or Hepatitis C RNA (HCV RNA) within 28 days prior to randomization
Pregnancy Test (WOCBP only)	X	Serum or urine to be done at screening visit and repeated within 24 hours prior to first dose of study therapy
Efficacy Assessment		
Baseline Tumor Imaging Assessment	X	CT of chest, and CT or MRI of abdomen, pelvis, upper urinary tract and all known or suspected sites of disease (including cystoscopy in subjects with upper GU primaries who still have bladder intact) within 28 days prior to randomization. MRI brain within 28 days prior to randomization for subjects with clinical suspicion or history of brain/leptomeningeal metastases.
IVRS		
Register Subject in IVRS	X	A call must be made to the IVRS to register subject after signing informed consent.

Table 5.1-2: Treatment Phase (for subjects receiving nivolumab/placebo)

Procedure	During Treatment On Day 1 of Every Cycle (Cycle = 2 weeks)	Notes
Safety Assessments		
Targeted Physical Examination	X	Targeted examination must include at a minimum the following body systems: Cardiovascular Gastrointestinal Pulmonary
Vital Signs	X	Including BP, HR and temperature. Obtain vital signs within 72 hours prior to each dose.
Physical Measurements (including performance status)	X	Weight and ECOG performance status. See Appendix 2 for ECOG Performance Status scale.
Review of Concomitant Medication	X	
Adverse Events Assessment	X	
Laboratory Tests	X	CBC w/differential and platelet count, Chemistry panel including: LDH, AST, ALT, ALP, T. Bili, BUN or serum urea level, creatinine, Ca++, Mg++, Na+, K+, Cl-, LDH, albumin, glucose, amylase, lipase. TSH (Reflex to Free T4, Free T3 for abnormal TSH result) to be performed every 6 weeks (every 3 cycles) Urine cytology as clinically indicated (eg, to confirm recurrence in the bladder) On-study local laboratory assessments should be done within 72 hours prior to each dose through Week 23 visit and every alternative dose thereafter. Liver function tests (AST, ALT, ALP, T. Bili) will be analyzed within 72 hours prior to each dose throughout the treatment period.
Pregnancy Test (WOCBP only)	X	Serum or urine pregnancy test to be done within 24 hours prior to first dose, and then every 4 weeks (+/– 1 week) regardless of dosing schedule, or more frequently/at a frequency per local regulations/requirements.

Table 5.1-2: Treatment Phase (for subjects receiving nivolumab/placebo)

Procedure	During Treatment On Day 1 of Every Cycle (Cycle = 2 weeks)	Notes
Efficacy Assessments		
Tumor Imaging Assessment	• Non-cystoscopy tumor imaging assessments will occur every 12 weeks from the date of first dose to Week 96 (ie, Week 12, 24, 36, 48, 60, 72, 84, 96; +/- 1 week), then every 16 weeks from Week 96 to Week 160 (ie, Week 112, 128, 144, 160; +/- 2 weeks), then every 24 weeks until non-urothelial tract recurrence or treatment is discontinued (whichever occurs later) for a maximum of 5 years (ie, Week 184, 208, 232, 256; +/- 4 weeks). • Non-cystoscopy tumor imaging assessments: CT of chest, and CT or MRI of abdomen, pelvis, upper urinary tract, and all known sites of disease. Use same imaging method as was used at screening/baseline. • Cystoscopy in subjects with upper GU primaries who still have bladder intact will occur in addition to other tumor imaging assessments every 12 weeks from the date of first dose to Week 48 (ie, Week 12, 24, 36, 48 +/- 1 week), then every 24 weeks from Week 48 to Week 96 (i.e. Week 72, 96; +/- 2 weeks), then every 48 weeks until non-urothelial tract recurrence or treatment is discontinued (whichever occurs later) for a maximum of 5 years (i.e. Week 96, 144, 192, 240; +/- 4 weeks).	
[redacted]		
[redacted]	[redacted]	
[redacted]	[redacted]	
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[redacted]	[redacted]	
[redacted]	[redacted]	
[redacted]	[redacted]	
[redacted]	[redacted]	

Table 5.1-2: Treatment Phase (for subjects receiving nivolumab/placebo)

Procedure	During Treatment On Day 1 of Every Cycle (Cycle = 2 weeks)	Notes
[redacted]	[redacted]	
[redacted]	[redacted]	
[redacted]		
[redacted]	[redacted]	
[redacted]	[redacted]	
Clinical Drug Supplies		
Randomization	X	Call IVRS for randomization (Tumor tissue submitted to central lab must be logged as received and PD-L1 results must be documented by the central lab in IVRS prior to randomization. Allow approximately 10 business days from the date of shipping for tissue to be received and processed.)
IVRS Drug Vial Assignment	X	Vials may be assigned up to 3 days prior to first dose date.
Dispense Study Drug	X	Within 3 days from vial allocation, the subject must receive the first dose of study medication. Subjects may be dosed no less than 12 days between doses.

Table 5.1-3: Follow-Up Period Following Discontinuation from Study Therapy			
Procedure	**Follow Up, Visits 1 and 2[a]**	**Survival Follow-Up Visits[b]**	**Notes**
Safety Assessments			
Targeted Physical Examination	X		To assess for potential late emergent study drug related issues Targeted examination must include at a minimum the following body systems: Cardiovascular Gastrointestinal Pulmonary
Adverse Events Assessment	X		In Survival Follow-Up period only to include toxicities from study therapy. Immune-mediated adverse drug reactions will be followed until resolution.
Review of Subsequent Therapy	X	X	Subsequent Cancer Therapy
[redacted]	[redacted]		[redacted]
Pregnancy Test (WOCBP only)	X		Serum or urine

Table 5.1-3: Follow-Up Period Following Discontinuation from Study Therapy

Procedure	Follow Up, Visits 1 and 2[a]	Survival Follow-Up Visits[b]	Notes
Efficacy Assessments			
Tumor Imaging Assessment	See note	See note	Only for subjects who enter the follow-up period without non-urothelial tract recurrence. • Non-cystoscopy tumor imaging assessments will occur every 12 weeks from the date of first dose to Week 96 (ie, Week 12, 24, 36, 48, 60, 72, 84, 96; +/- 1 week), then every 16 weeks from Week 96 to Week 160 (i.e. Week 112, 128, 144, 160; +/- 2 weeks), then every 24 weeks until non-urothelial tract recurrence or treatment is discontinued (whichever occurs later) for a maximum of 5 years (ie, Week 184, 208, 232, 256; +/- 4 weeks). • Non-cystoscopy tumor imaging assessments: CT of chest, and CT or MRI of abdomen, pelvis, upper urinary tract, and all known sites of disease. Use same imaging method as was used at screening/baseline. • Cystoscopy in subjects with upper GU primaries who still have bladder intact will occur in addition to other tumor imaging assessments every 12 weeks from the date of first dose to Week 48 (i.e. Week 12, 24, 36, 48 +/- 1 week), then every 24 weeks from Week 48 to Week 96 (i.e. Week 72, 96; +/- 2 weeks), then every 48 weeks until non-urothelial tract recurrence or treatment is discontinued (whichever occurs later) for a maximum of 5 years (i.e. Week 96, 144, 192, 240; +/- 4 weeks).
[redacted]			
[redacted]	[redacted]		[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]		[redacted]
[redacted]			
[redacted]	[redacted]	[redacted]	[redacted]

Table 5.1-3: Follow-Up Period Following Discontinuation from Study Therapy

Procedure	Follow Up, Visits 1 and 2[a]	Survival Follow-Up Visits[b]	Notes
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]			
[redacted]	[redacted]		[redacted]
[redacted]	[redacted]		[redacted]
Subject Status			
Survival Status		**X**	Section 3.6. Collect **every 3 months** in Survival Visits until death, lost to follow-up, or withdrawal of study consent. May be performed by phone contact or office visit. Additionally, data regarding subsequent anti-cancer therapy will also be collected.

a Subjects must be followed for at least 100 days after last dose of study therapy Follow-up visit #1 (FU1) occurs approximately 35 days (+/- 7 days) after the last dose or coinciding with the date of discontinuation (+/- 7 days) if date of discontinuation is greater than 35 days after last dose. Follow up visit #2 (FU2) occurs approximately 80 days (+/- 7 days) after FU1.

b Survival visits = every 3 months (+/- 7 days) from FU2 until the end of the study (5 years from the primary analysis of DFS). FU2 visits may be conducted during clinic visit or via the telephone.

c Laboratory toxicities (eg, suspected drug induced liver enzyme elevations) will be monitored during the follow-up phase via on site/local labs until all study drug related toxicities resolve, return to baseline, or are deemed irreversible.

5.1.1 Retesting During Screening or Lead-in Period

Laboratory parameters and/or assessments that are included in Table 5.1-1, Screening Procedural Outline may be repeated in an effort to find all possible well-qualified subjects. Consultation with the Medical Monitor may be needed to identify whether repeat testing of any particular parameter is clinically relevant.

5.2 Study Materials

- NCI CTCAE version 4.0
- Nivolumab IB
- Pharmacy Information Sheets
- Laboratory manuals for collection and handling of blood (including biomarker and immunogenicity) and tissue specimens;
- Site manual for operation of IVRS, including enrollment worksheets
- Manual for entry of local laboratory data
- Pregnancy Surveillance Forms
- PRO Instruments
- Manual describing process of sending images to corelab

5.3 Safety Assessments

At baseline, a medical history will be obtained to capture relevant underlying conditions. The baseline examinations should include signs and symptoms, weight, height, ECOG Performance Status, BP, HR and temperature should be performed within 72 hours prior to first dose. Concomitant medications will also be collected from within 14 days prior to first dose and through the study treatment period (See Table 5.1-1 and Table 5.1-2).

Baseline local laboratory assessments should be done within 14 days prior to the first dose and include: CBC w/differential, LFTs (ALT, AST, total bilirubin, alkaline phosphatase), BUN or serum urea level, creatinine, Ca, Mg, Na, K, Cl, LDH, glucose, and, if clinically indicated, urine cytology. Amylase, lipase, TSH, Free T4, Free T3, and Hep B and C testing (HBV sAg and HCV RNA or Ab) should be done within 28 days. Pregnancy testing for WOCBP (done locally) to be done within 24 hours prior to first dose, and then every 4 weeks (+ or – 1 week) regardless of dosing schedule, and at each safety follow up visit (Follow up visits 1 and 2). See Table 5.1-1, Table 5.1-2, and Table 5.1-3.

On-study local laboratory assessments should be done within 72 hours prior to each dose through Week 23 visit and every alternative dose thereafter. Liver function tests (AST, ALT, ALP, T. Bili) will be analyzed within 72 hours prior to each dose throughout the treatment period. Labs should be reviewed by investigator prior to treatment. Subjects will be evaluated for safety if they have received any study drug. Adverse events (AE) assessments will be performed continuously during the treatment phase. During the safety follow-up phase (Table 5.1-3) AE assessments

should be done in person. Once subjects reach the survival follow-up phase, either in-person visits or documented telephone calls or emails to assess the subject's status are acceptable.

Adverse events and laboratory values will be graded according to the NCI-CTCAE version 4.0.

On-study weight, ECOG performance status, and vital signs should be assessed at each on-study visit prior to nivolumab/placebo dosing. Vital signs should also be taken as per institutional standard of care prior to, during and after dosing. The start and stop time of the nivolumab infusion should be documented. Physical examinations are to be performed at treatment visits as clinically indicated. If there are any new or worsening clinically significant changes since the last exam, report changes on the appropriate non-serious or serious adverse event page.

Additional measures, including non-study required laboratory tests, should be performed as clinically indicated or to comply with local regulations. Laboratory toxicities (eg, suspected drug induced liver enzyme elevations) will be monitored during the follow-up phase via on site/local labs until all study drug related toxicities resolve, return to baseline or are deemed irreversible.

Oxygen saturation by pulse oximetry (optional) may be obtained prior to each dosing and at any time a subject has any new or worsening respiratory symptoms. If obtained, accurate recording and documentation of oxygen saturation at two different activity levels is important because drug-related pulmonary toxicity can present initially as lower than baseline oxygen saturation. A reading at rest and on exertion should be obtained at each time point. The extent of the exertion should be based on the judgment of the investigator, but should remain consistent for each individual subject throughout the study. If the subject's status changes, the investigator can alter the extent of exertion based on their medical judgment. If a subject shows changes on pulse oximetry or other pulmonary related signs (hypoxia, fever) or symptoms (eg, dyspnea, cough, fever) consistent with possible pulmonary adverse events, the subject should be immediately evaluated to rule out pulmonary toxicity. An algorithm for the management of suspected pulmonary toxicity can be found in the nivolumab Investigator's Brochure.

Some of the previously referred to assessments may not be captured as data in the eCRF. They are intended to be used as safety monitoring by the treating physician. Additional testing or assessments may be performed as clinically necessary or where required by institutional or local regulations.

5.4 Efficacy Assessments

Study evaluations will take place in accordance with the flow charts in Section 5. Baseline disease assessments should be performed within 28 days prior to randomization utilizing CT or MRI. In addition to chest, abdomen, pelvis, upper urinary tract, and all known sites of resected disease (including cystoscopy in subjects with upper GU primaries who still have bladder intact) should be assessed at baseline. Brain imaging (MRI except where contraindicated in which CT scan is acceptable) must be completed within 28 days prior to randomization for subjects with clinical suspicion of or known history of brain/leptomeningeal metastases at screening. Of note, screening cystoscopy in subjects who have an intact bladder should occur within 60 days prior to randomization. All suspect lesions identified during screening radiographic procedures should be

discussed with the Medical Monitor prior to randomization. Subjects will be evaluated for presence or continued lack of tumor until non-urothelial tract recurrence as below:

- Non-cystoscopy tumor imaging assessments will occur every 12 weeks from the date of first dose to Week 96 (ie, Week 12, 24, 36, 48, 60, 72, 84, 96; +/- 1 week), then every 16 weeks from Week 96 to Week 160 (ie, Week 112, 128, 144, 160; +/- 2 weeks), then every 24 weeks until non-urothelial tract recurrence or treatment is discontinued (whichever occurs later) for a maximum of 5 years (ie, Week 184, 208, 232, 256; +/- 4 weeks).
- Non-cystoscopy tumor imaging assessments: CT of chest, and CT or MRI of abdomen, pelvis, upper urinary tract, and all known sites of disease. Use same imaging method as was used at screening/baseline.
- Cystoscopy in subjects with upper GU primaries who still have bladder intact will occur in addition to other tumor imaging assessments every 12 weeks from the date of first dose to Week 48 (ie, Week 12, 24, 36, 48 +/- 1 week), then every 24 weeks from Week 48 to Week 96 (ie, Week 72, 96; +/- 2 weeks), then every 48 weeks until non-urothelial tract recurrence or treatment is discontinued (whichever occurs later) for a maximum of 5 years (ie, Week 144, 192, 240; +/- 4 weeks).

5.4.1 Definitions

Recurrence will be considered as any evidence of pathologic disease as described in section 5.4.3. Subjects that have lymph nodes of 10-14 mm in short axis at baseline, will be considered as having recurrence if those lymph nodes progress to ≥ 15 mm in short axis, or if new pathologic lesions are found. Confirmation of recurrence must be attempted as described in section 5.4.3.

The primary endpoint is DFS is defined as time from randomization until death from any cause or recurrence of tumor as described below:

- **Local, Urothelial Tract**: Any new urothelial carcinoma in the lower or upper urothelial tract, including lesions thought to be a second urothelial carcinoma primary will be considered recurrences.
  - Any new invasive urothelial carcinoma (defined as T2 or greater) in the lower or upper urothelial tract, including lesions thought to be a second urothelial carcinoma primary will be considered recurrences. Low-risk NMIBC will not be reported as a recurrence event, while high- and intermediate-risk NMIBC will be reported as a recurrence event.
    - Treatment with study drug may continue if the subject develops low-risk NMIBC that is removed at cystoscopy. The subject may continue study treatment if the subject develops intermediate-risk NMIBC and if intravesical chemotherapy or BCG is not required. Study treatment must be discontinued in the setting of any high-risk recurrence in the urothelial tract.

    Low-risk NMIBC is defined as low-grade lesions or papillary urothelial neoplasms of low malignant potential (PUNLMP; WHO/ISUP 2004 grading system), or TaG1 lesions (WHO 1973 grading system) that are less than 3 cm in diameter.

High-risk NMIBC is defined as any T1 lesion, any lesion containing carcinoma in situ (CIS) either alone or concomitantly with papillary disease (e.g. CIS with Ta/T1 lesions), and any Ta high-grade (TaHG; WHO/ISUP 2004 grading system) or TaG3 (WHO 1973 grading system) lesion.

Intermediate-risk NMIBC is defined as lesions not meeting the criteria of high-risk or low-risk.

For subjects with recurrent urothelial tract disease who are no longer eligible for study treatment, tumor imaging should continue until a non-urothelial tract recurrence is documented.

- **Local, Non-Urothelial Tract**: Any recurrence in pelvic soft tissue or involving pelvic nodes below the aortic bifurcation
- **Distant**: Any non-local recurrence

Suspect lesions: Suspect lesions identified radiographically during tumor assessments will be followed according to the defined schedule to determine if they represent recurrent urothelial cancer. If a suspect lesion is confirmed to be recurrent urothelial cancer on subsequent scans, the date of recurrence will be the date the suspect lesion was first identified. If a suspect lesion is identified during cystoscopy, it should be biopsied to determine if it is high-risk, and if so, would represent recurrent local urothelial cancer.

5.4.2 Methods of Measurements

- CT and MRI are an essential part of the work-up to establish recurrence. The following imaging assessments should be performed at pre-specified intervals: CT of chest, and CT or MRI of abdomen, pelvis, upper urinary tract and all known or suspected sites of disease (including cystoscopy in subjects with upper GU primaries who still have bladder intact).
- CT scans should be acquired with 5 mm slices with no intervening gap (contiguous).
- Should a subject have a contraindication for CT IV contrast, a non-contrast CT of the chest and a contrast enhanced MRI of the abdomen and pelvis may be obtained. MRIs should be acquired with slice thickness of < 5 mm with no gap (contiguous).
- Every attempt should be made to image each subject using an identical acquisition protocol on the same scanner for all imaging time points.
- PET alone will not be considered for the disease assessment. Complementary CT and/or MRI or biopsy must be performed in such cases.
  - Note: Use of CT component of a PET/CT scanner:

    Combined modality scanning such as with FDG-PET/CT is increasingly used in clinical care, and is a modality/technology that is in rapid evolution; therefore, the recommendations outlined here may change rather quickly with time. At present, low dose or attenuation correction CT portions of a combined FDG-PET/CT are of limited use in anatomically based efficacy assessments and it is therefore suggested that they should not

be substituted for dedicated diagnostic contrast enhanced CT scans for anatomically based tumor assessments. However, if a site can document that the CT performed as part of a FDG-PET/CT is of identical diagnostic quality to a diagnostic CT (with IV and oral contrast) then the CT portion of the FDG-PET/CT can be used for tumor assessments. Note, however, that the FDG-PET portion of the CT introduces additional data which may bias an investigator if it is not routinely or serially performed

5.4.3 Confirmation and Date of Recurrence

The first date when recurrence was observed is taken into account regardless of the method of assessment. Therefore recurrence will be declared for any lesion when:

- If recurrence is unequivocal (eg, multiple new measurable lesions, symptomatic or requires initiation of subsequent treatment prior to confirmation) confirmation with histology/cytology should be attempted, but not required.
- If recurrence is equivocal, lymph node only, solitary lesion, or in the urothelial tract, confirmation with histology/cytology must be attempted. Confirmation of a defined lesion on cystoscopy requires transurethral biopsy and, if necessary, retrograde study and biopsy. If risk of biopsy is too high or biopsy not feasible, either a follow-up CT or MRI scan showing progressive disease or PET/CT demonstrating unequivocal FDG uptake must confirm recurrence. Follow-up (confirmatory) scan should occur 4-12 weeks after the initial scan. The date of initial scan showing recurrence will count as recurrence.
- Any pathological evidence of malignancy denotes recurrence (eg, if scans never attempted). Positive urine cytology (eg, positive Urovision or similar urine assay) alone does not constitute the basis for recurrence of disease. Tumor markers or auto-antibodies alone cannot be used to document recurrence.
- If both pathology and imagining were done and recurrence/malignancy confirmed, the date of recurrence is the date to which ever examination came first.
- When biopsies are performed for the purpose of documenting urothelial cancer recurrence, the pathology reports are to be submitted to corelab for a collect and hold. This includes biopsies performed during cystoscopy.

[redacted]

5.6.1 Tumor Tissue Specimens

Pre-treatment tumor tissue specimens in the form of a paraffin embedded block or a minimum of 10 unstained slides will be submitted for central PD-L1 IHC assessment prior to randomization. These biopsy samples should be from the most recently resected site of disease. PD-L1 stained tissue sections will be assessed by a pathologist and membranous PD-L1 expression scored in tumor and immune cells if a minimum of a hundred (100) evaluable tumor cells are present. Subjects with tumor samples containing less than a hundred tumors cells per tissue section will not be randomized, but subjects with positive, negative or indeterminate (membrane staining is obscured by high cytoplasmic staining or melanin content) PD-L1 expression will be stratified based on their expression. PD-L1 expression level or indeterminate status (as assessed by central lab) will be logged into IVRS by the central laboratory prior to randomization. Allow approximately 10 business days from the date of shipping for tissue to be received and processed. Allow for this time in planning for randomization. If PD-L1 expression results have not been logged into IVRS by the central laboratory, randomization will not be allowable through IVRS.

In addition, this pre-treatment tumor sample may be used to assess other putative predictive biomarkers of nivolumab efficacy and/or to better characterize the tumor-immune microenvironment within the resected tissue. Various molecular markers with potential predictive value for the treatment of urothelial cancer with nivolumab and other immunotherapies are currently under investigation and may be assessed in this study. These tumor tissue biomarkers include, but are not limited to PD-L1, PD-L2, 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. These pre-treatment tumor samples may also be used to further characterize the tumor-immune microenvironment through assessment of markers that may be associated with the efficacy of nivolumab, including but not limited to other T cell checkpoint receptors and ligands (eg, Lag-3, Tim-3) intratumoral immune cell subsets, including macrophages, natural killer (NK) cells and B cells.

Tumor tissue samples may also be collected upon recurrence. This sample may be used for the assessment of markers implicated in resistance to immunotherapeutic agents, including but not limited to other T cell checkpoint receptors and ligands (eg, Lag-3, Tim-3) and intratumoral immune cell subsets, including but not limited to, T regulatory cells and myeloid derived suppressor cells. These samples may also be used to investigate the effect of nivolumab on the expression of potentially relevant predictive and/or prognostic urothelial cancer biomarkers. Both the pre-treatment tumor sample and the sample collected upon recurrence may be retrospectively profiled for gene expression/mutation status, as well as for the expression of other immune or urothelial cancer related genes, RNAs, miRNA and proteins, or for the presence of immune cell populations using a variety of methodologies inclusive of, but not limited to IHC, qRT-PCR, genetic mutation detection and fluorescent in-situ hybridization (FISH).

[redacted]

6 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 study drug 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 study drug, whether or not considered related to the study drug.

The causal relationship to study drug is determined by a physician and should be used to assess all adverse events (AE). The causal 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.)

6.1 Serious Adverse Events

A S***erious 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 [eg, 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. (See Section 6.6 for the definition of potential DILI.)

Suspected transmission of an infectious agent (eg, pathogenic or nonpathogenic) via the study drug is an SAE.

Although pregnancy, overdose, cancer, and potential drug induced liver injury (DILI) are not always serious by regulatory definition, these events must be handled as SAEs. (See Section 6.1.1 for reporting pregnancies).

Any component of a study endpoint that is considered related to study therapy (eg, death is an endpoint, if death occurred due to anaphylaxis, anaphylaxis must be reported) should be reported as SAE (see Section 6.1.1 for reporting details).

NOTE:

The following hospitalizations are not considered SAEs in BMS clinical studies:

- 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 (eg, 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).
- Admission for administration of anticancer therapy in the absence of any other SAEs (applies to oncology protocols)

6.1.1 Serious Adverse Event Collection and Reporting

Sections 5.6.1 and 5.6.2 in the Investigator Brochure (IB) represent the Reference Safety Information to determine expectedness of serious adverse events for expedited 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 during the screening period and within 100 days of discontinuation of dosing.

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 during the screening period and within 100 days of discontinuation of dosing. Subjects who are randomized and never treated with study drug, must have SAEs collected for 30 days from the date of randomization. If applicable, SAEs must be collected that relate to any later protocol-specified procedure (eg, a follow-up skin biopsy).

The investigator should report any SAE that occurs after these time periods and that is believed to be related to study drug or protocol-specified procedure.

An SAE report should be completed for any event where doubt exists regarding its seriousness.

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.

SAEs, whether related or not related to study drug, and pregnancies must be reported to BMS (or designee) within 24 hours of becoming aware of the event. SAEs must be recorded on the SAE Report Form; pregnancies on a Pregnancy Surveillance Form (electronic or paper forms). The preferred method for SAE data reporting collection is through the eCRF. The paper SAE/pregnancy surveillance forms are only intended as a back-up option when the eCRF system is not functioning. In this case, the paper forms are to be transmitted via email or confirmed facsimile (fax) transmission to:

SAE Email Address: Refer to Contact Information list.

SAE Facsimile Number: Refer to Contact Information list.

For studies capturing SAEs through electronic data capture (EDC), electronic submission is the required method for reporting. The paper forms should be used and submitted immediately, only in the event the electronic system is unavailable for transmission. When paper forms are used, the original paper forms are to remain on site.

SAE Telephone Contact (required for SAE and pregnancy reporting): Refer to Contact Information list.

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.

6.2 Nonserious Adverse Events

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

6.2.1 Nonserious Adverse Event Collection and Reporting

The collection of nonserious AE information should begin at initiation of study drug. 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.

Nonserious AEs should be followed to resolution or stabilization, or reported as SAEs if they become serious (see Section 6.1.1). 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. All identified nonserious AEs must be recorded and described on the nonserious AE page of the CRF (paper or electronic).

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.

Every adverse event must be assessed by the investigator with regard to whether it is considered immune-mediated. For events which are potentially immune-mediated, additional information will be collected on the participant's case report form.

Completion of supplemental CRFs may be requested for AEs and/or laboratory abnormalities that are reported/identified during the course of the study.

6.2.2 Adverse Events of Interest

Definition of immune-mediated adverse events (IMAEs)

Immune-mediated AEs are specific events (that include pneumonitis, diarrhea/colitis, hepatitis, nephritis/renal dysfunction, rash, and endocrine (adrenal insufficiency, hypothyroidism/thyroiditis, hyperthyroidism, diabetes mellitus, and hypophysitis) for which subjects received immunosuppressive medication for treatment of the event, with the exception of endocrine events (hypothyroidism/thyroiditis, hyperthyroidism, hypophysitis, diabetes mellitus, adrenal insufficiency), which are included regardless of treatment since these events are often managed without immunosuppression.

Immune-mediated adverse events are AEs consistent with an immune-mediated mechanism or immune-mediated component for which non-inflammatory etiologies (eg, infection or tumor progression) have been ruled out. IMAEs can include events with an alternate etiology which were exacerbated by the induction of autoimmunity. Information supporting the assessment will be collected on the participant's case report form.IMAEs include events, regardless of causality,

occurring within 100 days of the last dose. IMAEs are limited to subjects who received immunosuppressive medication for treatment of the event, with the exception of endocrine events (hypothyroidism/thyroiditis, hyperthyroidism, hypophysitis, diabetes mellitus, adrenal insufficiency), which are included regardless of treatment since these events are often managed without immunosuppression.

Table 6.2.2-1 below provides a summary of the IMAEs category and their respective PTs.

Table 6.2.2-1: Preferred Terms Included in Analysis of IMAEs to Support Warnings and Precautions

IMAE Category	PTs included under IMAE Category
Pneumonitis	Pneumonitis, Interstitial lung disease
Diarrhea/Colitis	Diarrhea, Colitis, Enterocolitis
Hepatitis	Hepatotoxicity, Hepatitis, Hepatitis acute, Autoimmune hepatitis, AST increased, ALT increased, Bilirubin increased, ALP increased
Adrenal insufficiency	Adrenal insufficiency
Hypothyroidism/Thyroiditis	Hypothyroidism, Thyroiditis Thyroiditis acute (collapsed with thyroiditis for frequency), Autoimmune thyroiditis (collapsed with thyroiditis for frequency)
Hyperthyroidism	Hyperthyroidism
Hypophysitis	Hypophysitis
Diabetes mellitus	Diabetes mellitus, Diabetic ketoacidosis
Nephritis and renal dysfunction	Nephritis, Nephritis allergic, Tubulointerstitial nephritis, Acute renal failure, Renal failure, Increased creatinine
Rash	Rash, Rash maculopapular

6.3 Laboratory Test Result Abnormalities

The following laboratory test result abnormalities should be captured on the nonserious AE CRF page or SAE Report Form (paper or electronic) as appropriate:

- Any laboratory test result that is clinically significant or meets the definition of an SAE
- Any laboratory test result abnormality that required the subject to have study drug discontinued or interrupted
- Any laboratory test result abnormality that required the subject to receive specific corrective therapy.

It is expected that wherever possible, the clinical rather than laboratory term would be used by the reporting investigator (eg, anemia versus low hemoglobin value).

6.4 Pregnancy

If, following initiation of the study drug, it is subsequently discovered that a study subject is pregnant or may have been pregnant at the time of study exposure, including during at least 5 half-lives after product administration, the investigator must immediately notify the BMS Medical Monitor/designee of this event and complete and forward a Pregnancy Surveillance Form to BMS Designee within 24 hours and in accordance with SAE reporting procedures described in Section 6.1.1 .

In most cases, the study drug will be permanently discontinued in an appropriate manner (eg, dose tapering if necessary for subject safety).

In the rare event that the benefit of continuing study drug is thought to outweigh the risk, after consultation with BMS, the pregnant subject may continue study drug after a thorough discussion of benefits and risk with the subject

If the study will also include women who are NOT of childbearing potential, include the following paragraph. Otherwise, please delete the next paragraph only.

Protocol-required procedures for study discontinuation and follow-up must be performed on the subject unless contraindicated by pregnancy (eg, x-ray studies). Other appropriate pregnancy follow-up procedures should be considered if indicated.

The investigator must immediately notify the BMS (or designee) Medical Monitor of this event and complete and forward a Pregnancy Surveillance Form to BMS (or designee) within 24 hours and in accordance with SAE reporting procedures described in Section 6.1.1.

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.

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.

6.5 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. Overdoses meeting the regulatory definition of an SAE will be reported as SAEs (see Section 6.1.1 for reporting details).

6.6 Potential Drug Induced Liver Injury (DILI)

Specific criteria for identifying potential DILI have not been identified for this protocol. Standard medical practice in identifying and monitoring hepatic issues should be followed.

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 (see Section 6.1.1 for reporting details).

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 AT 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.

6.7 Other Safety Considerations

Any significant worsening noted during interim or final physical examinations, electrocardiogram, x-ray filming, any other potential safety assessment required or not required by protocol should also be recorded as a nonserious or serious AE, as appropriate, and reported accordingly.

7 DATA MONITORING COMMITTEE AND OTHER EXTERNAL COMMITTEES

A Data Monitoring Committee (DMC) will be established to provide oversight of safety and efficacy considerations in protocol CA209274. Additionally, the DMC will provide advice to the sponsor regarding actions the committee deems necessary for the continuing protection of subjects enrolled in the study. The DMC will be charged with assessing such actions in light of an acceptable benefit/risk profile for nivolumab. The DMC will act in an advisory capacity to BMS and will monitor subject safety and evaluate the available efficacy data for the study. Details regarding the responsibilities of the DMC including frequency of meetings will be included in the DMC charter. The oncology therapeutic area of BMS has primary responsibility for design and conduct of the study.

When required adjudicated events will be submitted to the DMC and Health Authorities for review on a specified timeframe in accordance with the adjudication documentation.

8 STATISTICAL CONSIDERATIONS

8.1 Sample Size Determination

The sample size for this study is based on a comparison of the DFS distribution between subjects randomized to receive nivolumab and subjects randomized to receive placebo. There will be two co-primary comparisons: in subjects with PD-L1 expression level ≥ 1% and in all randomized subjects with an alpha allocation of 2.5% (two-sided) each.

The prevalence of subjects with PD-L1 expression level ≥ 1% is expected to be around 42% (Section 1.1.4.6) and see Section 3.1 for information around anticipated number of subjects.

In time-to-events trials, the number of events and power may typically be calculated assuming an exponential distribution in each treatment arm. However for DFS, a meaningful number of long-term disease-free survivors may be observed. As a consequence, the DFS curves may not follow an exponential decay and a flattening of the curves may be observed toward the end of the tail (Section 1.1.4.9)**.** Consequently, an exponential cure rate distribution was used to calculate the sample size.

The exponential cure rate distribution can be described with following formula:

$$S(t) = p + (1 - p) * \{e^{-\alpha t}\},$$

where p is the cure rate and α is the parameter of the exponential distribution for the non-cured population.

Based on historical data, median DFS distribution in the control arm is assumed to be 12 months with a 5 year DFS rate of 32% used as the cure rate[1] (ie, p=0.32 and α=0.11). It is also assumed that DFS distribution in control arm does not depend on the PD-L1 expression level. Cure rates in subjects with PD-L1 expression level ≥ 1% and in the all randomized population for the experimental arm are targeted to be 54% and 47% respectively while non cured population is assumed to follow same distribution as in the control arm. It is assumed that the effect of nivolumab vs. placebo will be delayed. A study of nivolumab vs. ipilimumab in metastatic melanoma (CheckMate 238[51]) suggested a 3-month delayed effect for nivolumab, therefore the model used for the experimental arm also assumes a 3-month delayed effect in subjects with PD-L1 expression level ≥1% and in the all randomized population for the experimental arm.

Approximately 700 subjects will be randomized in 1:1 ratio to nivolumab arm and control arm respectively.

- Approximately 410 DFS events in all randomized subjects will provide around 87% power to detect an average HR of 0.72 with an overall type I error of 2.5% (two-sided)
- Approximately 162 DFS events in subjects with PD-L1 expression level ≥ 1% (~294 subjects) will provide around 80% power to detect an average HR of 0.61 with an overall type I error of 2.5% (two-sided).

The target average hazard ratios were obtained via simulation using above modeling.

It is expected that the required number of events in each population will be reached when all subjects will have at least a minimum of 17 months of follow-up.

An interim DFS analysis will also be performed when 85% of DFS events in each population will be observed (ie, 348 and 137 DFS events in all randomized and in subjects with PD-L1 expression level ≥ 1%, respectively). The alpha level for DFS will be adjusted for the planned interim analysis using Lan-DeMets alpha spending function with the O'Brien-Fleming type of boundary in East v6.

Assuming an average accrual rate of 16 subjects per month, the accrual will take approximately 43 months. The total duration of the study from start of randomization to final analysis of DFS is

expected to be 60 months (43 months of accrual + 17 months of follow-up). DFS analyses in all randomized population and in subjects with PD-L1 expression level ≥ 1% are projected to occur 45 months after start of the study for the interim analyses and 60 months (43 months of accrual + 17 months of follow-up) for the final analyses (Table 8.1-1 and Table 8.1-2).

It is expected that interim DFS analysis in each population will occur at the same time. However, because the DFS event rate pattern may be different between all randomized population and subjects with PD-L1 expression level ≥ 1%, the interim DFS analysis of each population might also occur separately.

Table 8.1-1: Schedule of Analyses of Primary Endpoint in all randomized population

	Interim DFS analysis	**Final DFS analyses**
Conditions	When 348 events of DFS are observed in all randomized subjects	When 410 events of DFS are observed in all randomized subjects
Population	All randomized subjects	All randomized subjects
Expected timing	45 months	60 months (43 months of accrual + 17 months of follow-up)
Nominal significance level/Power	0.01349149	0.02108499 / 87%
Lower boundary for statistical significance	**Observed hazard ratio of 0.76**	**Observed hazard ratio of 0.79**

Table 8.1-2: Schedule of Analyses of Primary Endpoint in subjects with PD-L1 expression level ≥ 1%

	Interim DFS analysis	**Final DFS analyses**
Conditions	When 137 events of DFS are observed in subjects with PD-L1 expression level ≥ 1%	When 162 events of DFS are observed in subjects with PD-L1 expression level ≥ 1%
Population(s)	Subjects with PD-L1expression level ≥ 1%	Subjects with PD-L1expression level ≥ 1%
Expected timing	45 months	60 months (43 months of accrual + 17 months of follow-up)
Nominal significance level / Power	0.01349149	0.02108499 / 80%
Lower boundary for statistical significance	**Observed hazard ratio of 0.65**	**Observed hazard ratio of 0.69**

Key secondary endpoint of OS will be formally compared (in subjects with PD-L1 expression level ≥ 1% and all randomized subjects) using a hierarchical procedure in each population (see Section 8.5).

8.2 Populations for Analyses

- Enrolled subjects: All subjects who signed an informed consent form and were registered into the IVRS.
- Randomized subjects: All enrolled subjects who were randomized. This dataset will be used for baseline demographics and efficacy analyses
- Randomized subjects with PD-L1 expression level ≥ 1%: All randomized subjects with baseline tumor sample testing per IHC result ≥ 1% membranous staining in tumor cell. This dataset will be used for baseline demographics and efficacy analyses.
- Treated subjects: All randomized subjects who received at least one dose of study drug. This dataset will be used for safety analyses.
- Treated subjects with PD-L1 expression level ≥ 1%: Randomized subjects with PD-L1expression level ≥ 1% who received at least one dose of study drug. This dataset will be used for safety analyses.

[redacted]

8.3 Endpoints

8.3.1 Primary Endpoint(s)

The primary endpoint of DFS will be programmatically determined based on the disease recurrence date provided by the investigator and is defined as the time between the date of randomization and the date of first recurrence as defined in section 5.4.1 (local urothelial tract, local non-urothelial tract or distant) or death (of any cause), whichever occurs first. (Note: a subject who dies without reported recurrence will be considered to have recurred on the date of death.) For subjects who remain alive and whose disease has not recurred, DFS will be censored on the date of last evaluable disease assessment.

Detailed censoring rules for the primary definition of DFS are presented in Table 8.3.1-1. Sensitivity analyses of DFS will be described in the statistical analysis plan

Table 8.3.1-1: Censoring scheme used in primary definition of DFS

Situation	Date of Progression or Censoring	Outcome
Disease at baseline	Date of randomization	Event
Any recurrence (ie local urothelial tract, local non urothelial tract or distant)	Date of first recurrence	Event
Death from any cause without recurrence	Date of death	Event
No baseline disease assessment	Date of randomization	Censored

Table 8.3.1-1: Censoring scheme used in primary definition of DFS

Situation	Date of Progression or Censoring	Outcome
No on-study disease assessments and no death	Date of randomization	Censored
No recurrence and no death	Date of last evaluable disease assessment	Censored
New anticancer therapy, tumor directed radiotherapy, or tumor directed surgery received without recurrence reported prior to or on the same day*	Date of last evaluable disease assessment prior to or on the same date of initiation of subsequent therapy	Censored
Second non-urothelial primary cancer reported without recurrence reported prior to or on the same day	Date of last evaluable disease assessment prior to or on the same date of diagnosis of second non-urothelial primary cancer	Censored

*Further details regarding the censoring scheme will be provided in the statistical analysis plan.

Disease assessments will occur as below:

- Non-cystoscopy tumor imaging assessments will occur every 12 weeks from the date of first dose to Week 96 (ie, Week 12, 24, 36, 48, 60, 72, 84, 96; +/- 1 week), then every 16 weeks from Week 96 to Week 160 (i.e. Week 112, 128, 144, 160; +/- 2 weeks), then every 24 weeks until non-urothelial tract recurrence or treatment is discontinued (whichever occurs later) for a maximum of 5 years (ie, Week 184, 208, 232, 256; +/- 4 weeks).
- Non-cystoscopy tumor imaging assessments: CT of chest, and CT or MRI of abdomen, pelvis, upper urinary tract, and all known sites of disease. Use same imaging method as was used at screening/baseline.
- Cystoscopy in subjects with upper GU primaries who still have bladder intact will occur in addition to other tumor imaging assessments every 12 weeks from the date of first dose to Week 48 (ie, Week 12, 24, 36, 48 +/- 1 week), then every 24 weeks from Week 48 to Week 96 (ie, Week 72, 96; +/- 2 weeks), then every 48 weeks until non-urothelial tract recurrence or treatment is discontinued (whichever occurs later) for a maximum of 5 years (ie, Week 144, 192, 240; +/- 4 weeks).

This endpoint will be analyzed in two different populations (co-primary): Subjects with PD-L1 expression level ≥ 1% and all randomized subjects.

8.3.2 Secondary Endpoints

8.3.2.1 Overall Survival (OS)

The key second secondary endpoint of Overall Survival (OS) is defined as the time between the date of randomization and the date of death (of any cause). For subjects without documentation of death, OS will be censored on the last date the subject was known to be alive. OS will be followed continuously while subjects are on the study drug and every 3 months via in-person or phone contact after subjects discontinue the study drug.

This endpoint will be analyzed in two different populations (co-primary): Subjects with PD-L1expression level ≥1% and all randomized subjects.

8.3.2.2 Non-Urothelial Tract Recurrence Free-Survival (NUTRFS)

The secondary endpoint NUTRFS is defined as the time between the date of randomization and the date of first local non urothelial tract or distant recurrence or death (of any cause), whichever occurs first. For subjects who remain alive and local non urothelial tract or distant recurrence-free, NUTRFS will be censored on the date of last evaluable disease assessment.

Detailed censoring rules for the primary definition of NUTRFS are presented in Table 8.3.2.2-1.

Table 8.3.2.2-1: Censoring scheme used in primary definition of NUTRFS

Situation	Date of Progression or Censoring	Outcome
Disease at baseline	Date of randomization	Event
Non-Urothelial Recurrence (ie local non-urothelial recurrence or distant metastasis)	Date of first recurrence	Event
Death from any cause without recurrence	Date of death	Event
No baseline disease assessment	Date of randomization	Censored
No on-study disease assessments and no death	Date of randomization	Censored
No recurrence and no death	Date of last evaluable disease assessment	Censored
New anticancer therapy, tumor directed radiotherapy, or tumor directed surgery received without recurrence reported prior to or on the same day *	Date of last evaluable disease assessment prior to or on the same date of initiation of subsequent therapy	Censored
Second non-urothelial primary cancer reported without recurrence reported prior to or on the same day	Date of last evaluable disease assessment prior to or on the same date of diagnosis of second non-urothelial primary cancer	Censored

*Further details regarding the censoring scheme will be provided in the statistical analysis plan.

Disease assessments as stated in Section 8.3.1.

This endpoint will be analyzed in two different populations (co-primary): Subjects with PD-L1expression level ≥ 1% and all randomized subjects.

8.3.2.3 Disease Specific Survival (DSS)

The secondary endpoint DSS is defined as the time between the date of randomization and the date of death due to disease (urothelial cancer). For subjects without documentation of death, DSS will be censored on the last date the subject was known to be alive. DSS will be followed continuously as part of OS follow-up while subjects are on the study drug and every 3 months via in-person or phone contact after subjects discontinue the study drug.

This endpoint will be analyzed in two different populations (co-primary): Subjects with PD-L1expression level ≥ 1% and all randomized subjects.

[redacted]

8.4 Analyses

8.4.1 Demographics and Baseline Characteristics

Demographic and baseline laboratory results will be summarized by treatment arm as randomized using descriptive statistics. Analysis will be conducted on subjects with PD-L1expression level ≥ 1% and repeated on the all randomized subjects.

8.4.2 Efficacy Analyses

8.4.2.1 Primary Endpoint Methods

DFS distribution in all randomized subjects and subjects with PD-L1expression level ≥ 1% will be compared between treatment group using a two-sided stratified log-rank test at the overall significance level of 2.5% (two-sided) each.

The HR and corresponding two-sided 100x (1-adjusted α)% confidence intervals (CIs) will be estimated in a Cox proportional hazards model using treatment as a single covariate, stratified by PD-L1 status (only in the all randomized population comparison), prior neo-adjuvant cisplatin chemotherapy, positive lymph node status.

DFS curves will be estimated using the KM product-limit method. Median DFS and the corresponding two-sided 95% CIs using the log-log transformation will be computed. In additional, DFS rate at 6 months, 1 year and 2 years (and yearly after depending on the follow-up) and the corresponding two-sided 95% CIs using the log-log transformation will be computed.

Similar descriptive analyses will also be performed in subjects with PD-L1 expression level < 1%.

The assumption of proportional hazards in the Cox regression model will be examined and additional parametric models will be further investigated in case of non-proportionality.

8.4.2.2 Secondary Endpoint Methods

The analyses for secondary endpoints of NUTRFS, DSS and OS will be performed in all randomized subjects as well as in subjects with PD-L1expression level ≥ 1%.

The key secondary endpoint of OS distribution will be compared between treatment groups using a two-sided stratified log-rank test at the overall significance level of 2.5% (two-sided) each. These comparisons will be tested using hierarchical procedure in each population.

The OS HR and corresponding two-sided 100x (1-adjusted α)% CIs will be estimated in a Cox proportional hazards model using treatment as a single covariate, stratified by PD-L1 status (only in the all randomized population comparison), prior neo-adjuvant cisplatin chemotherapy, positive lymph node status.

The NUTRFS HR and corresponding two-sided 95% CIs will be estimated in a Cox proportional hazards model using treatment as a single covariate, stratified by PD-L1 status (only in the all randomized population comparison), prior neo-adjuvant cisplatin chemotherapy, positive lymph node status.

NUTRFS and OS distribution curves will be estimated using Kaplan-Meier methodology by treatment arm. Median values and the corresponding two-sided 95% CIs using the log-log transformation will also be computed. NUTRFS and OS rates at 6 months, 1 year and 2 years (and yearly after depending on the follow-up) and the corresponding two-sided 95% CIs using the log-log transformation will be computed.

Cumulative incidence of DSS[51] will be also estimated.

No formal comparison will be done for NUTRFS and DSS secondary endpoints.

8.4.3 Safety Analyses

The safety analysis will be performed in treated subjects with PD-L1expression level ≥ 1 % as well as in all treated subjects. Descriptive statistics of safety will be presented using NCI CTCAE version 4.0 by treatment arm. Adverse events, drug-related AEs, SAEs and drug-related SAEs will be tabulated using worst grade per NCI CTCAE v.4.0 criteria by system organ class and preferred term. On-study lab parameters including hematology, chemistry, liver function and renal function will be summarized using worst grade per NCI CTCAE v.4.0 criteria.

8.5 Interim Analyses

The final analysis of DFS in each population will be performed at the same time when 410 and 162 events of DFS are observed in all randomized subjects and in subjects with PD-L1 expression level ≥1%, respectively (defined as analysis timepoint T_2).

An interim DFS analysis (defined as analysis timepoint T_1) will be also performed when 85% of DFS events in each population will be observed (ie, 348 and 137 DFS events in all randomized subjects and in subjects with PD-L1 expression level ≥ 1%, respectively). The alpha level for DFS will be adjusted for the planned interim analysis using Lan-DeMets alpha spending function with the O'Brien-Fleming type of boundary in East v6.

The secondary endpoint of OS will be formally compared (in subjects with PD-L1 expression level ≥ 1% and all randomized subjects) using a hierarchical procedure in each population. Overall hierarchical approach as discussed in Glimm et al. [52] will be followed with overall alpha of 2.5% (two-sided) using Lan-DeMets alpha spending function with the O'Brien-Fleming type of boundary in East v6 for each endpoint.

In all randomized subjects

OS could be formally compared

a) at the final analysis of DFS (defined as T_2) that will occur after 410 DFS events have been observed, approximately 230 OS events should be observed at this timepoint.

b) after 303 OS events have been observed (defined as T_3)..

c) after 404 OS events have been observed (defined as T_4).

This testing procedure is also summarized in Figure 8.5-1.

Approximately 404 OS events in all randomized subjects will provide approximately 87% power to detect an HR of 0.71 with an overall type I error of 2.5% (two-sided). This corresponds to a median increase from 4.6 years to 6.5 years under exponential assumption. Two interim analyses are planned for OS in all randomized subjects at ~57% (ie, 230 events) and at 75% (ie, 303 events) information fractions. It is projected that an observed hazard ratio of 0.66, 0.73 and 0.79 or less would results in a statistically significant OS improvement of nivolumab at the first interim, second interim or final analysis, respectively.

In subjects with PD-L1 expression level ≥ 1%

Similar procedure will applied for the secondary endpoints comparisons in subjects with PD-L1 expression ≥ 1 and is summarized in Figure 8.5-2.

OS could be formally compared

a) at the final analysis of DFS (defined as T_2) that will occur after 162 DFS events have been observed, approximately 91 OS events should be observed at this timepoint.

b) after 125 OS events have been observed (defined as T_3).

c) after 166 OS events have been observed (defined as T_4).

Approximately 166 OS events in subjects with PD-L1 expression level ≥ 1% will provide approximately 82% power to detect an HR of 0.61 with an overall type I error of 2.5% (two-sided). This corresponds to a median increase from 4.6 years to 7.5 years under exponential assumption. Two interim analyses are planned for OS in all randomized subjects with PD-L1 expression level ≥ 1% at ~55% (ie, 91 events) and at 75% (ie, 125 events) information fractions. It is projected that an observed hazard ratio of 0.51, 0.61 and 0.70 or less would results in a statistically significant OS improvement of nivolumab at the first interim, second interim or final analysis, respectively.

The interim and final DFS analysis are projected to occur around 45 and 60 months after the start of accrual (T_1, T_2), respectively followed by T_3 (second interim analysis of OS) around 75 months and T_4 (final analysis of OS) around 105 months after the start of accrual.

Figure 8.5-1: Hierarchical procedure with group sequential testing in the all randomized population

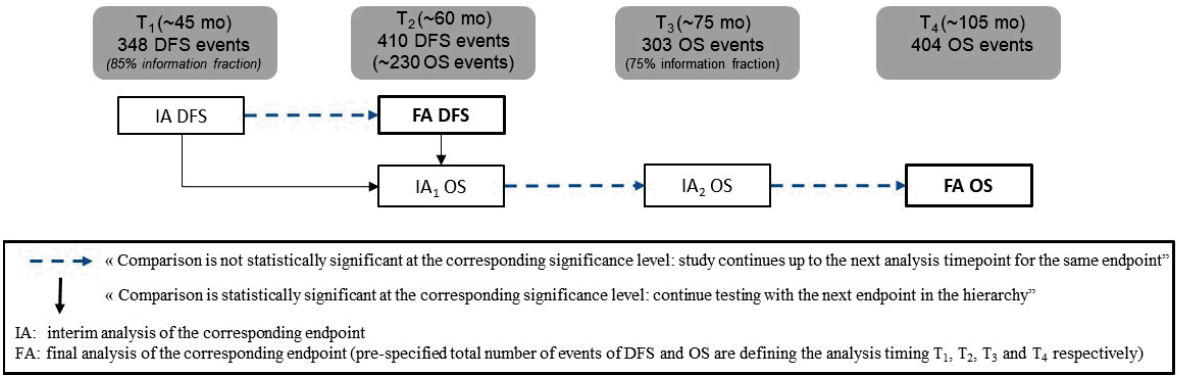
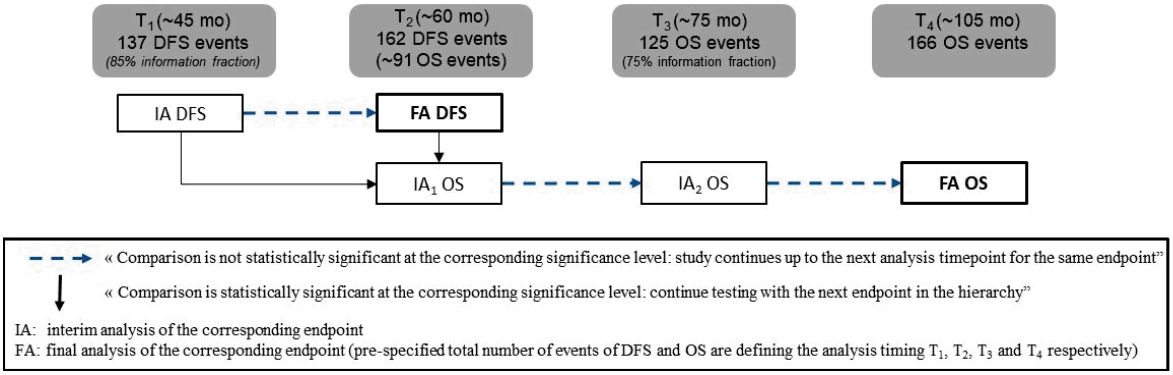


Figure 8.5-2: Hierarchical procedure with group sequential testing in the subjects with PD-L1 >=1%



9 STUDY MANAGEMENT

9.1 Compliance

9.1.1 Compliance with the Protocol and Protocol Revisions

The study shall be conducted as described in this approved protocol. All revisions to the protocol must be discussed with, and be prepared by, BMS. The investigator should not implement any deviation or change to the protocol without prior review and documented approval/favorable opinion from the IRB/IEC of an amendment, except where necessary to eliminate an immediate hazard(s) to study subjects.

If a deviation or change to a protocol is implemented to eliminate an immediate hazard(s) prior to obtaining IRB/IEC approval/favorable opinion, as soon as possible the deviation or change will be submitted to:

- IRB/IEC for review and approval/favorable opinion
- BMS
- Regulatory Authority(ies), if required by local regulations

Documentation of approval signed by the chairperson or designee of the IRB(s)/IEC(s) must be sent to BMS.

If an amendment substantially alters the study design or increases the potential risk to the subject: (1) the consent form must be revised and submitted to the IRB(s)/IEC(s) for review and approval/favorable opinion; (2) the revised form must be used to obtain consent from subjects currently enrolled in the study if they are affected by the amendment; and (3) the new form must be used to obtain consent from new subjects prior to enrollment.

If the revision is done via an administrative letter, investigators must inform their IRB(s)/IEC(s).

9.1.2 Monitoring

BMS representatives will review data centrally to identify potential issues to determine a schedule of on-site visits for targeted review of study records.

Representatives of BMS must be allowed to visit all study site locations periodically to assess the data quality and study integrity. On site they will review study records and directly compare them with source documents, discuss the conduct of the study with the investigator, and verify that the facilities remain acceptable.

In addition, the study may be evaluated by BMS internal auditors and government inspectors who must be allowed access to CRFs, source documents, other study files, and study facilities. BMS audit reports will be kept confidential.

The investigator must notify BMS promptly of any inspections scheduled by regulatory authorities, and promptly forward copies of inspection reports to BMS.

9.1.2.1 Source Documentation

The Investigator is responsible for ensuring that the source data are accurate, legible, contemporaneous, original and attributable, whether the data are hand-written on paper or entered electronically. If source data are created (first entered), modified, maintained, archived, retrieved, or transmitted electronically via computerized systems (and/or any other kind of electronic devices) as part of regulated clinical trial activities, such systems must be compliant with all applicable laws and regulations governing use of electronic records and/or electronic signatures. Such systems may include, but are not limited to, electronic medical/health records (EMRs/EHRs), adverse event tracking/reporting, protocol required assessments, and/or drug accountability records).

When paper records from such systems are used in place of electronic format to perform regulated activities, such paper records should be certified copies. A certified copy consists of a copy of original information that has been verified, as indicated by a dated signature, as an exact copy having all of the same attributes and information as the original.

9.1.3 Investigational Site Training

Bristol-Myers Squibb will provide quality investigational staff training prior to study initiation. Training topics will include but are not limited to: GCP, AE reporting, study details and procedure, electronic CRFs, study documentation, informed consent, and enrollment of WOCBP.

9.2 Records

9.2.1 Records Retention

The investigator must retain all study records and source documents for the maximum period required by applicable regulations and guidelines, or institution procedures, or for the period specified by BMS, whichever is longer. The investigator must contact BMS prior to destroying any records associated with the study.

BMS will notify the investigator when the study records are no longer needed.

If the investigator withdraws from the study (eg, relocation, retirement), the records shall be transferred to a mutually agreed upon designee (eg, another investigator, IRB). Notice of such transfer will be given in writing to BMS.

9.2.2 Study Drug Records

It is the responsibility of the investigator to ensure that a current disposition record of study drug (inventoried and dispensed) is maintained at the study site to include investigational product and the following non-investigational product(s) placebo. Records or logs must comply with applicable regulations and guidelines and should include:

- amount received and placed in storage area
- amount currently in storage area
- label identification number or batch number
- amount dispensed to and returned by each subject, including unique subject identifiers

- amount transferred to another area/site for dispensing or storage
- non-study disposition (eg, lost, wasted)
- amount destroyed at study site, if applicable
- amount returned to BMS
- retain samples for bioavailability/bioequivalence, if applicable
- dates and initials of person responsible for Investigational Product dispensing/accountability, as per the Delegation of Authority Form.

BMS will provide forms to facilitate inventory control if the investigational site does not have an established system that meets these requirements.

9.2.3 Case Report Forms

An investigator is required to prepare and maintain adequate and accurate case histories designed to record all observations and other data pertinent to the investigation on each individual treated or entered as a control in the investigation. Data that are derived from source documents and reported on the CRF must be consistent with the source documents or the discrepancies must be explained. Additional clinical information may be collected and analyzed in an effort to enhance understanding of product safety. CRFs may be requested for AEs and/or laboratory abnormalities that are reported or identified during the course of the study.

For sites using the BMS electronic data capture tool, electronic CRFs will be prepared for all data collection fields except for fields specific to SAEs and pregnancy, which will be reported on the paper or electronic SAE form and Pregnancy Surveillance form, respectively. Spaces may be left blank only in those circumstances permitted by study-specific CRF completion guidelines provided by BMS.

The confidentiality of records that could identify subjects must be protected, respecting the privacy and confidentiality rules in accordance with the applicable regulatory requirement(s).

The investigator will maintain a signature sheet to document signatures and initials of all persons authorized to make entries and/or corrections on CRFs.

The completed CRF, including any paper or electronic SAE/pregnancy CRFs, must be promptly reviewed, signed, and dated by the investigator or qualified physician who is a subinvestigator and who is delegated this task on the Delegation of Authority Form. For electronic CRFs, review and approval/signature is completed electronically through the BMS electronic data capture tool. The investigator must retain a copy of the CRFs including records of the changes and corrections.

Each individual electronically signing electronic CRFs must meet BMS training requirements and must only access the BMS electronic data capture tool using the unique user account provided by BMS. User accounts are not to be shared or reassigned to other individuals.

9.3 Clinical Study Report and Publications

A Signatory Investigator must be selected to sign the clinical study report.

For this protocol, the Signatory Investigator will be selected as appropriate based on the following criteria:

Select only the criteria that are applicable from the list below:

Subject recruitment (eg, among the top quartile of enrollers)

Involvement in trial design

The data collected during this study are confidential and proprietary to BMS. Any publications or abstracts arising from this study require approval by BMS prior to publication or presentation and must adhere to BMS's publication requirements as set forth in the approved clinical trial agreement (CTA). All draft publications, including abstracts or detailed summaries of any proposed presentations, must be submitted to BMS at the earliest practicable time for review, but at any event not less than 30 days before submission or presentation unless otherwise set forth in the CTA. BMS shall have the right to delete any confidential or proprietary information contained in any proposed presentation or abstract and may delay publication for up to 60 days for purposes of filing a patent application.

10 GLOSSARY OF TERMS

Term	Definition
Adverse Reaction	An adverse event that is considered by either the investigator or BMS as related to the investigational product
Unexpected Adverse Reaction	An adverse reaction, the nature or severity of which is not consistent with the applicable product information (eg, Investigator Brochure for an unapproved investigational product)
Serious Adverse Event	Serious adverse event defined as 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; 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 [eg, 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.). For reporting purposes only, BMS also considers the occurrence of pregnancy, overdose (regardless of association with an AE), and cancer as important medical events.

11 LIST OF ABBREVIATIONS

Term	Definition
AE	adverse event
AIDS	Acquired Immune Deficiency Syndrome
ALP	alkaline phosphatase
ALT	alanine aminotransferase
AST	aspartate aminotransferase
AT	aminotransaminase
AUC	area under the concentration-time curve
β-HCG	beta-human chorionic gonadotrophin
BMS	Bristol-Myers Squibb
BP	blood pressure
BUN	blood urea nitrogen
C	Celsius
Ca++	calcium
Cavgss	time averaged steady state concentration
CBC	complete blood count
CFR	Code of Federal Regulations
CI	confidence interval
C1-	chloride
CLcr	creatinine clearance
Cmax, CMAX	maximum observed concentration
Cminss	steady state trough concentration
CMV	Cytomegalovirus
CR	complete response
CRC	colorectal cancer
CRF	Case Report Form, paper or electronic
CTCAE	common terminology criteria adverse event
Ct-DNA	chloroplast DNA
CTLA-4	cytotoxic T-lymphocyte-associated protein 4
Cv	coefficient of variation

Term	Definition
DC	Dendritic Cell
DMFS	distant metastasis free survival
DFS	disease free survival
dL	deciliter
DMC	Data Monitoring Committee
DSS	disease specific survival
ECG	electrocardiogram
ECOG PS	Eastern Cooperative Oncology Group Performance Status
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture
Eg	exempli gratia (for example)
EORTC QLQ-C30	European Organization for Research and Treatment of Care Core Quality of Life Questionnaire
ESR	Expedited Safety Report
EQ-5D-3L	Three Level European Organization for Research and Treatment of Care Quality of Life Questionnaire 5 Dimensions
EU	European Union
FACS	Fluorescence-activated cell sorting
FDA	Food and Drug Administration
FFPE	formalin fixed, paraffin embedded
FSH	follicle stimulating hormone
GCP	Good Clinical Practice
GFR	glomerular filtration rate
GI	gastrointestinal
H	hour
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HCV	hepatitis C virus
HIPAA	Health Insurance Portability and Accountability Act
HIV	Human Immunodeficiency Virus
HR	heart rate

Term	Definition
HRQoL	Health related quality of life
HRT	hormone replacement therapy
HRT	hormone replacement therapy
IB	Investigator Brochure
ICF	Informed Consent Form
ICH	International Conference on Harmonization
Ie	id est (that is)
IEC	Independent Ethics Committee
Ig	immunoglobulin
IHC	immunohistochemistry
IMG	immunoglobulin
IMP	investigational medicinal products
IND	Investigational New Drug Exemption
I-O	Immuno-oncology
IRB	Institutional Review Board
ITSM	immunoreceptor tyrosine-based switch motif
IU	International Unit
IUC	Invasive urothelial carcinoma
IUD	intrauterine device
IV	intravenous
IVRS	Interactive voice response system
K+	potassium
Kg	kilogram
KM	Kaplan-Meier
LDH	lactate dehydrogenase
LFT	liver function test
LRC	locoregional control
LRDFS	locoregional disease free survival
mAbs	monoclonal antibodies
MDSC	Myeloid derived suppressor cells

Term	Definition
MEL	melanoma
Mg	milligram
Mg++	magnesium
MIBC	muscle invasive bladder cancer
mL	milliliter
MLR	Mixed Lymphocyte Reaction
µg	microgram
MST	Medical Safety Team
MVAC	methotrexate, vinblastine, doxorubicin, and cisplatin
N	number of subjects or observations
Na+	sodium
N/A	not applicable
NCCN	National Comprehensive Cancer Network
NIMP	non-investigational medicinal products
NSCLC	non-small cell lung cancer
NUTRFS	non-urothelial tract recurrence free survival
ONO	Ono Pharmaceutical Company, Ltd
ORR	overall response rate
OS	overall survival
PBMCs	Peripheral blood mononuclear cells
PD	pharmacodynamics
PD-1	programmed cell death receptor-1
PD-L1	programmed cell death receptor-ligand 1
PFSR	progression free survival rate
PK	pharmacokinetics
PPK	population pharmacokinetics
PR	partial response
PRO	patient reported outcome
PSA	prostate specific antigen
RC	radical cystectomy

Term	Definition
RCC	renal cell carcinoma
RNU	radical nephroureterectomy
RU	radical ureterectomy
SAE	serious adverse event
SD	standard deviation
SNPs	single nucleotide polymorphisms
SOP	Standard Operating Procedures
SWOG	Southwest Oncology Group
TAO	Trial Access Online, the BMS implementation of an EDC capability
T.Bili	total bilirubin
TCR	T-cell receptor
Tregs	T regulatory cells
TSH	thyroid stimulating hormone
TTR	time to response
US	United States
UTUC	upper tract urothelial cancer
VEGF	vascular endothelial growth factor
WBC	white blood cell
WOCBP	women of childbearing potential

APPENDIX 3 WOMEN OF CHILDBEARING POTENTIAL DEFINITIONS AND METHODS OF CONTRACEPTION

DEFINITIONS

Woman of Childbearing Potential (WOCBP)

A woman is considered fertile following menarche and until becoming post-menopausal unless permanently sterile. Permanent sterilization methods include hysterectomy, bilateral salpingectomy, and bilateral oophorectomy.

Women in the following categories are not considered WOCBP

- Premenarchal
- Premenopausal female with 1 of the following:
  - Documented hysterectomy
  - Documented bilateral salpingectomy
  - Documented bilateral oophorectomy

Note: Documentation can come from the site personnel's review of the participant's medical records, medical examination, or medical history interview.

- Postmenopausal female
  - A postmenopausal state is defined as 12 months of amenorrhea in a woman over age 45 years in the absence of other biological or physiological causes. In addition, females under the age of 55 years must have a serum follicle stimulating hormone, (FSH) level > 40 mIU/mL to confirm menopause.

Note: Females treated with hormone replacement therapy, (HRT) are likely to have artificially suppressed FSH levels and may require a washout period in order to obtain a physiologic FSH level. The duration of the washout period is a function of the type of HRT used. The duration of the washout period below are suggested guidelines and the investigators should use their judgement in checking serum FSH levels.

- 1 week minimum for vaginal hormonal products (rings, creams, gels)
- 4 week minimum for transdermal products
- 8 week minimum for oral products

Other parenteral products may require washout periods as long as 6 months. If the serum FSH level is > 40 mIU/ml at any time during the washout period, the woman can be considered postmenopausal.

CONTRACEPTION GUIDANCE FOR FEMALE PARTICIPANTS OF CHILD BEARING POTENTIAL

One of the highly effective methods of contraception listed below is required during study duration and until the end of relevant systemic exposure, defined as 5 months after the end of study treatment.

Local laws and regulations may require use of alternative and/or additional contraception methods.

Highly Effective Contraceptive Methods That Are User Dependent *Failure rate of <1% per year when used consistently and correctly.*[a]
• Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation[b] – oral – intravaginal – transdermal
• Progestogen-only hormonal contraception associated with inhibition of ovulation[b] – oral – injectable
Highly Effective Methods That Are User Independent
• Implantable progestogen-only hormonal contraception associated with inhibition of ovulation [b] • Intrauterine device (IUD)[c] • Intrauterine hormone-releasing system (IUS)[c] • Bilateral tubal occlusion
• Vasectomized partner *A vasectomized partner is a highly effective contraception method provided that the partner is the sole male sexual partner of the WOCBP and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used.*
• Sexual abstinence *Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study drug. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant.* • It is not necessary to use any other method of contraception when complete abstinence is elected. • WOCBP participants who choose complete abstinence must continue to have pregnancy tests, as specified in Section 2. • Acceptable alternate methods of highly effective contraception must be discussed in the event that the WOCBP participants chooses to forego complete abstinence

NOTES:

[a] Typical use failure rates may differ from those when used consistently and correctly. Use should be consistent with local regulations regarding the use of contraceptive methods for participants participating in clinical studies.

[b] Hormonal contraception may be susceptible to interaction with the study drug, which may reduce the efficacy of the contraceptive method. Hormonal contraception is permissible only when there is sufficient evidence that the IMP and other study medications will not alter hormonal exposures such that contraception would be ineffective or result in increased exposures that could be potentially hazardous. In this case, alternative methods of contraception should be utilized.

[c] Intrauterine devices and intrauterine hormone releasing systems are acceptable methods of contraception in the absence of definitive drug interaction studies when hormone exposures from intrauterine devices do not alter contraception effectiveness

Less Than Highly Effective Contraceptive Methods That Are User Dependent

Failure rate of >1% per year when used consistently and correctly.

- Male or female condom with or without spermicide. Male and female condoms cannot be used simultaneously
- Diaphragm with spermicide
- Cervical cap with spermicide
- Vaginal Sponge with spermicide
- Progestogen-only oral hormonal contraception, where inhibition of ovulation is not the primary mechanism of action

Unacceptable Methods of Contraception

- Periodic abstinence (calendar, symptothermal, post-ovulation methods)
- Withdrawal(coitus interruptus).
- Spermicide only
- Lactation amenorrhea method (LAM)

CONTRACEPTION GUIDANCE FOR MALE PARTICIPANTS WITH PARTNER(S) OF CHILD BEARING POTENTIAL.

Male participants with female partners of childbearing potential are eligible to participate if they agree to the following during the treatment and until the end of relevant systemic exposure.

- Inform any and all partner(s) of their participation in a clinical drug study and the need to comply with contraception instructions as directed by the investigator.
- Male participants are required to use a condom for study duration and until the end of relevant systemic exposure defined as 7 months after the end of treatment in the male participant.
- Female partners of males participating in the study to consider use of effective methods of contraception until the end of relevant systemic exposure, defined as 7 months after the end of treatment in the male participant.

- Male participants with a pregnant or breastfeeding partner must agree to remain abstinent from penile vaginal intercourse or use a male condom during each episode of penile penetration during the treatment and until 7 months after the end of treatment.
- Refrain from donating sperm for the duration of the study treatment and for 7 months after the end of treatment.

COLLECTION OF PREGNANCY INFORMATION

Guidance for collection of Pregnancy Information and outcome of pregnancy on the Pregnancy Surveillance Form is provided in Sections 6.4 and 9.2.3 and the Appendix for Adverse Events and Serious Adverse Events Definitions and procedures for Evaluating, Follow-up and Reporting.