A Randomized, Double-Blinded, Phase II Study of Maintenance Pembrolizumab versus Placebo after First-line Chemotherapy in Patients with Metastatic Urothelial Cancer

Hoosier Cancer Research Network
GU14-182

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Funding Support and Pembrolizumab Provided By
Merck Sharp & Dohme Corp. ("Merck")

Investigational New Drug (IND) ID#: 127340

NCT# NCT02500121

Initial Protocol Version: 07AUG2015
Protocol Amendment Version Date:
19FEB2016
13APR2016
18JUN2016
02AUG2016
21MAR2017
01DEC2017
12NOV2018
05NOV2019

PROTOCOL SIGNATURE PAGE

Protocol title: A Randomized, Double-Blinded, Phase II Study of Maintenance Pembrolizumab versus Placebo after First-line Chemotherapy in Patients with Metastatic Urothelial Cancer

VERSION DATE: 05NOV2019

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

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

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Signature of Investigator Date

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Investigator Name (printed)

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SYNOPSIS

TITLE	A Randomized, Double-Blinded, Phase II study of Maintenance Pembrolizumab versus Placebo after First-line Chemotherapy in Patients with Metastatic Urothelial Cancer
SHORT TITLE	Testing the PD-1 inhibitor pembrolizumab after initial chemotherapy in patients with metastatic bladder cancer
PHASE	II
OBJECTIVES	**Primary Objective** The primary objective will be to determine the progression-free survival (PFS) as per immune-related RECIST (irRECIST) among subjects with metastatic urothelial cancer (mUC) treated with pembrolizumab versus placebo as maintenance therapy after up to 8 cycles of first-line chemotherapy. **Secondary Objectives** • Determine the 6-month PFS as per irRECIST • Determine the 6-month PFS as per irRECIST among the subsets of subjects with PD-L1 positive and PD-L1 negative tumors treated with pembrolizumab versus placebo. • Determine the PFS as per irRECIST among the subsets of subjects with PD-L1 positive and PD-L1 negative tumors treated with pembrolizumab versus placebo • Determine the PFS as per RECIST 1.1 among subjects treated with pembrolizumab versus placebo • Determine the objective response rate (ORR) by irRECIST and RECIST 1.1 in subjects on maintenance pembrolizumab versus placebo with measurable disease • Determine the ORR by irRECIST and RECIST 1.1 in subjects receiving pembrolizumab after progressing on placebo • Determine overall survival (OS) in subjects treated with pembrolizumab versus placebo • Determine the hazard ratios (HRs) with respect to both PFS and OS comparing subjects treated with pembrolizumab versus placebo • Determine the restricted mean survival time (RMST) in subjects treated with pembrolizumab versus placebo • Determine durations of response in subjects treated with pembrolizumab versus placebo • Determine the safety of pembrolizumab administration in this patient population **Exploratory Objectives** • Determine the PFS and 6mPFS rate among subjects without visceral metastatic disease randomized to pembrolizumab versus placebo

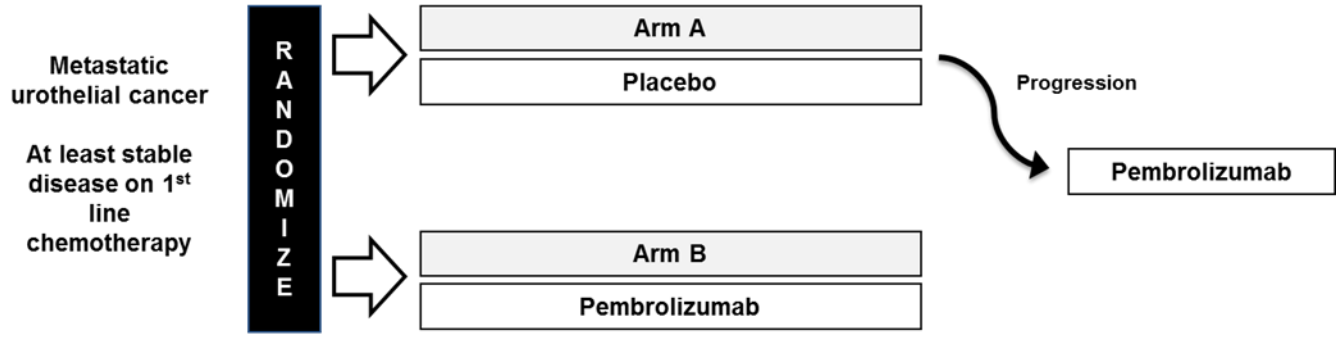
	• Compare PD-L1 expression in primary tumor tissue and metastatic post first-line chemotherapy tumor tissue in a subgroup of subjects. • Correlate immune infiltrates in tumor tissue with response rate, progression-free survival, and overall survival in subjects receiving pembrolizumab versus placebo • Determine the repertoire of humoral responses and correlate with response rate, progression-free survival, and overall survival • Determine the induction of T cell responses and correlate with response rate, progression-free survival, and overall survival • Correlate genomic alterations with response rate, progression-free survival, and overall survival • Correlate tobacco history with PFS in subjects receiving pembrolizumab versus placebo
STUDY DESIGN	This is a multi-institutional, randomized, placebo controlled, double-blinded phase II trial.
NUMBER OF SUBJECTS	N = 108
PARTICIPATING CENTERS	Up to 30 centers in Hoosier Cancer Research Network
ELIGIBILITY CRITERIA	Inclusion: 1. Written informed consent and HIPAA authorization for release of personal health information. **NOTE:** HIPAA authorization may be included in the informed consent or obtained separately. 2. Age ≥ 18 years at the time of consent. 3. ECOG Performance Status (PS) of ≤ 1 within 14 days prior to registration for protocol therapy. 4. Histological or cytological evidence of urothelial cancer of the bladder, urethra, ureter, or renal pelvis. Differentiation with variant histologies (e.g., squamous cell differentiated) will be permitted provided that the predominant histology is urothelial carcinoma. 5. Metastatic and/or unresectable (cT4b) disease 6. Must have achieved an objective response (CR/PR) or stable disease (SD) upon completion of scheduled treatment. 7. Subjects may have had up to 8 cycles of standard first-line platinum-based chemotherapy for mUC (e.g., as per NCCN guidelines). Able to commence study treatment within 2 to 6 weeks of receiving last dose of first-line chemotherapy. 8. All subjects must have adequate archival tissue available prior to registration (i.e., at least 20 unstained slides or paraffin block). If acceptable archival tissue is not available, the subject must be willing to consent to providing a core or excisional biopsy for research prior to registration for protocol therapy. If archival tissue

	is not available and there are no sites amenable to biopsy, enrollment must be discussed with the sponsor-investigator on a case by case basis. 9. Adequate laboratory values obtained within 14 days prior to registration for protocol therapy. (see protocol for details) 10. Female subjects of childbearing potential must have a negative serum pregnancy within three days of registration for protocol therapy. 11. Sexually active pre-menopausal women of childbearing potential must be willing to use an adequate method of contraception or be surgically sterile, or abstain from heterosexual activity from the point of registration through 120 days after the last dose of study drug. Subjects of childbearing potential are those who have not been surgically sterilized or have not been free from menses for > one year. 12. Male subjects of childbearing potential must agree to use an adequate method of contraception starting with the first dose of study drug through 120 days after the last dose of study drug. <u>Exclusion</u> 13. More than 1 line of prior chemotherapy for metastatic or locally advanced disease (prior neoadjuvant/adjuvant chemotherapy is allowed). 14. Current or past participation in a study of an investigational agent or using an investigational device within four weeks of registration for protocol therapy. 15. Diagnosis of immunodeficiency or treatment with systemic steroid therapy or any other form of immunosuppressive therapy within seven days of registration for protocol therapy. 16. Prior chemotherapy, targeted small molecule therapy, or radiation therapy within two weeks prior to registration for protocol therapy. Note: If subjects have undergone major surgery, they must have adequately recovered from the toxicity and/or complications from the intervention prior to starting protocol therapy. 17. Known additional malignancy that is progressing or requires active treatment. Exceptions include basal cell carcinoma of the skin, squamous cell carcinoma of the skin, or in situ cervical cancer that has undergone potentially curative therapy. 18. Known active central nervous system (CNS) metastases and/or carcinomatous meningitis. Subjects with previously treated brain metastases may participate provided they are stable (without evidence of progression by imaging for at least four weeks prior to registration for protocol therapy and any neurologic symptoms have returned to baseline), have no evidence of new or enlarging brain metastases, and are not using steroids for at least seven days prior to registration for protocol therapy.

	19. Active autoimmune disease requiring systemic treatment within the past three months or a documented history of clinically severe autoimmune disease, or a syndrome that requires systemic steroids or immunosuppressive agents. Exceptions include: subjects with vitiligo or resolved childhood asthma/atopy. Subjects who require intermittent use of bronchodilators or local steroid injections, and subjects with hypothyroidism who are stable on hormone replacement or Sjögren's syndrome are eligible for the study. 20. Has a history of (non-infectious) pneumonitis that required steroids or current pneumonitis. 21. Active infection requiring systemic therapy. 22. History or current evidence of any condition, therapy, or laboratory abnormality that might confound the results of the trial, interfere with the subject's participation for the full duration of the trial, or is not in the best interest of the subject to participate, in the opinion of the site investigator. 23. Known psychiatric or substance abuse disorders that would interfere with cooperation with the requirements of the trial. 24. Pregnant or breastfeeding, or expecting to conceive or father children within the projected duration of the trial, starting with the screening period through 120 days after the last dose of protocol therapy. 25. Prior therapy with an anti-PD-1, anti-PD-L1, anti-PD-L2, anti-CD137, or anti-Cytotoxic T-lymphocyte-associated antigen-4 (CTLA-4) antibody (including ipilimumab or any other antibody or drug specifically targeting T-cell co-stimulation or checkpoint pathways). Examples include nivolumab, MPDL3280, etc. 26. Known history of Human Immunodeficiency Virus (HIV) (HIV 1/2 antibodies). 27. Known active Hepatitis B (e.g., HBsAg reactive) or Hepatitis C (e.g., HCV RNA [qualitative] is detected). 28. Recipient of a live vaccine within 30 days prior to registration for protocol therapy. 29. Unresolved toxicity (i.e., > Grade 1 or above baseline) due to previously administered agents. Exception includes: Subjects with ≤ Grade 2 neuropathy are eligible for the study.
STATISTICAL CONSIDERATIONS	<u>Sample size calculation and analysis plan</u> We assume that the treatment group will experience three phases in terms of treatment effect: no effect, partial effect, and full effect. Specifically, we assume that before month 2, there is no treatment effect and after month 3 there is full treatment effect. In terms of hazard ratio, it is 1 before month 2, and a target value θ <1 after month 3. The decrease of the hazard ratio from 1 to θ between month 2 and 3 does not need to be specified and can take any pattern.

	We set the target value θ of the full treatment effect hazard ratio as 0.462. This target value is determined from the following rationale. The 12 months PFS is 6.2% for the control arm and 16.8% for the treatment arm from the KEYNOTE-045 trial. Assuming a constant hazard for the control group, we can obtain the hazard for the control arm is 0.232 for PFS from the KEYNOTE-45 trial, we assume the treatment reaches it full effect around month 8. This corresponds to a full treatment effect hazard ratio of 0.462. The sample size is determined by inverting the test statistic proposed by Zucker and Lakatos (1990). We set the type I error as 0.05 and power as 80%. Assuming the study duration is 3 years, the required total sample size based on one-sided test is at least 104 evaluable subjects (~52 per group). Therefore, the sample size is inflated to 108 to account for potential non-evaluable patients/early drop out. Censoring is assumed uniformly between month 6 and the end of study. Stratification factors for randomization: Presence of visceral metastatic disease (lung, liver, or bone or other organs vs. lymph node only) at the time of initiation of first-line chemotherapy, and response to first-line chemotherapy (CR/PR vs. SD).
ESTIMATED ENROLLMENT PERIOD	24 to 36 months
ESTIMATED STUDY DURATION	36 to 48 months is the estimated study duration. However, subjects will be followed per guidelines in Section 7.4.

SCHEMA


Metastatic urothelial cancer
At least stable disease on 1st line chemotherapy
RANDOMIZE
Arm A
Placebo
Progression
Pembrolizumab
Arm B
Pembrolizumab

1. BACKGROUND AND RATIONALE

1.1 Current therapies for metastatic urothelial cancer are inadequate

Standard first-line treatment for metastatic urothelial (bladder) cancer involves platinum-based combination therapy. While urothelial cancer is a relatively chemotherapy sensitive malignancy, median survival is only approximately 14 months.[1–3] These findings highlight a critical need to develop approaches that build on the chemosensitivity of urothelial cancer to achieve durable responses.

1.2 Bladder cancer is an immunogenic malignancy

Prior studies have shown that bladder cancer specimens harbor tumor infiltrating lymphocytes.[4,5] Immunohistochemical staining for intratumoral CD8 T cells in tissue samples from 69 patients with bladder cancer (pT2-T4) demonstrated that higher numbers of CD8 tumor infiltrating lymphocytes correlated with superior disease-free survival ($P < 0.001$) and overall survival ($P = 0.018$).[4] The cancer-testis family of antigens, characterized by both potent immunogenicity and a restricted expression pattern in normal adults, are overexpressed in bladder cancer. [6–8] In an analysis of a panel of cancer-testis antigens, >75% of bladder cancer specimens expressed at least one cancer-testis antigen.[8] A range of other antigens and neoantigens have been explored (and are currently being explored) as therapeutic targets in bladder cancer for protein and peptide vaccines and drug-immunoconjugates (e.g., HER-2, MUC-1, CEA, HCG, survivin, etc).

1.3 Despite the immunogenicity of bladder cancer, patients with bladder cancer also exhibit tumor-associated immunologic tolerance.[9–11]

Bladder cancer specimens have been shown to be infiltrated by T regulatory cells (Tregs) and to express high levels of inhibitory cytokines.[10] Notably, Tregs have been shown to diminish cancer-testis antigen vaccine-induced antigen-specific effector T cell responses in patients.[12]

1.4 Several lines of evidence support the importance of immune-checkpoint blockade as a therapeutic strategy for the treatment of advanced urothelial cancer.

Blockade of immune checkpoints is among the most promising approaches to activating therapeutic antitumour immunity. Immune checkpoints comprise multiple inhibitory pathways that are critical to the immune system's maintenance of self-tolerance and modulation of the duration and amplitude of immune responses. However, tumors co-opt certain immune checkpoints as a major mediator of immune resistance. The first immune checkpoints to achieve clinical translation include anti-CTLA-4 and anti-PD-1 (or anti-PD-L1) antibodies. These checkpoints play different roles during the immune response-CTLA4 predominantly regulates T cell activation whereas PD-1 predominantly regulates effector T cell activity within peripheral tissue and tumors.[13]

PD-1 and PD-L1 are overexpressed in bladder cancer specimens and correlate with clinical outcomes. In an analysis of 280 bladder cancer specimens, PD-L1 was expressed on 20% of pT2 specimens, 30% of pT3-4 specimens, and expression was significantly associated with higher tumor grade and stage.[14] A larger study of 318 bladder cancer specimens revealed that expression of PD-L1 by urothelial cancer cells (P <0.001) and PD-1 by tumor infiltrating lymphocytes (p=0.012) were significantly associated with pathologic stage.[15] In addition, in the subset of patients with organ-confined disease, PD-L1 expression independently predicted all-cause mortality after cystectomy (HR 3.18; 95% CI 1.74-5.79; P < 0.001; Figure 1).

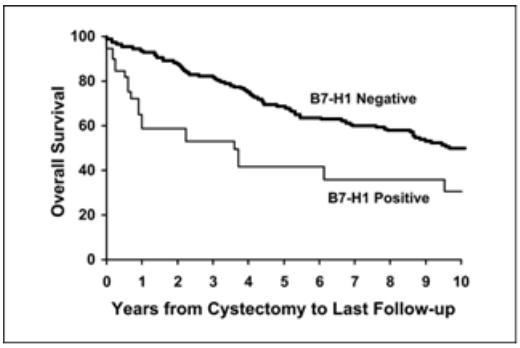


Figure 1. Association of PD-1 expression and outcomes in patients with muscle-invasive urothelial cancer (from Boorjian et al, Clin Cancer Res, 2008)

In a syngeneic (MB49) subcutaneous mouse model of bladder cancer, blocking CTLA-4 or PD-1 demonstrated anticancer effects.[16]

1.5 Combining chemotherapy with immune checkpoint blockade may result in additive or synergistic effects

Combining chemotherapy with immune checkpoint blockade may result in synergistic activity due to (a) release of tumor antigens as a result of tumor cell killing with cytotoxics, resulting in "auto-vaccination" and (b) depletion of tumor promoting cellular subsets with cytotoxic chemotherapy (e.g., Tregs, myeloid derived suppressor cells). Indeed, several preclinical models have supported this notion. Jure-Kunkel et al demonstrated synergy with the administration of gemcitabine in combination with CTLA-4 blockade in several syngeneic (mouse) xenografts – in a CT-26 colon cancer model, CTLA-4 blockade alone demonstrated no activity, gemcitabine alone demonstrated only modes activity, while the combination resulted in complete regressions in 5/8 animals.[17] Treatment with the combination was shown to increase levels of activated CD4 and CD8 T cells while decreasing the number of myeloid derived suppressor cells. Furthermore, mice achieving complete regression with the combination rejected subsequent tumor rechallenge consistent with the induction of a memory immune response.

1.6 "Switch maintenance" is an ideal setting for combining immune checkpoint blockade and chemotherapy in metastatic urothelial cancer

The optimal sequence of chemotherapy and immune checkpoint blockade in the management of advanced solid tumors remains to be defined. However, concurrent therapy may pose both practical (toxicities) and mechanistic (myelosuppressive and lymphodepleting effects of chemotherapy) challenges. The "maintenance" setting, presents an ideal clinical setting to further develop a sequential combination approach given:

1. Patients with at least stable disease to initial chemotherapy may be more likely to experience tumor cell kill and "auto-vaccination". In a contemporary series of patients treated with gemcitabine plus cisplatin, approximately 75% of patients achieved at least stable disease (at least partial responses in ~40%).[18]

2. In our international outcomes database of patients with urothelial cancer, among 1435 patients who received first-line chemotherapy for mUC, only 596 (42%) went on to receive second-line chemotherapy.[19] These data suggest substantial patient "drop off" from first to second-line therapy and the potential to impact the course of the disease in a more meaningful way with the earlier integration of noncross-resistant therapies.

3. The maintenance setting facilitates enrollment of both "cisplatin-eligible" and "cisplatin-ineligible" patients, at least partially addressing this accrual barrier to urothelial cancer studies.[2,20,21]

4. While time-to-event endpoints are most appropriate in this setting, objective responses are still evaluable for the majority of patients enrolled (excluding the small subset that achieved a complete response to first-line chemotherapy).

5. Particularly relevant to the question of timing of chemotherapy and immune checkpoint blockade, allowing cross-over to immune checkpoint blockade at progression in patients randomized to placebo may facilitate insights into the activity (and immunomodulatory effects) of PD-1 blockade in patients with shorter versus longer intervals from receipt of cytotoxic therapy.

1.7 Pembrolizumab is a novel antibody that blocks the interactions between PD-1 and PD-L1

Pembrolizumab is a potent and highly selective humanized monoclonal antibody (mAb) of the IgG4/kappa isotype designed to directly block the interaction between PD-1 and its ligands, PD-L1 and PD-L2. Pembrolizumab strongly enhances T-lymphocyte immune responses in cultured blood cells from healthy human donors, cancer patients, and primates. In T-cell activation assays using human donor blood cells, the EC50 (concentration where 50% of the maximum effect is achieved) has been ~0.1 to 0.3 nM. In addition to interleukin-2 (IL-2), tumor necrosis factor alpha, interferon gamma, and levels of other cytokines were found to be modulated by pembrolizumab. The antibody potentiates existing immune responses only in the presence of antigen and does not nonspecifically activate T-cells. Using an anti-murine PD-1 analog antibody, PD-1 blockade has been shown to significantly inhibit tumor growth in a variety of syngeneic murine tumor models.

Recent data with anti-PD-1 antibodies, including pembrolizumab and nivolumab (BMS-936558), have validated PD-1 as an attractive target for clinical intervention and have provided proof of concept for anti-PD-1 mAbs in several malignancies. Nivolumab showed an overall response rate of approximately 28% in patients with advanced melanoma and 27% in patients with renal carcinoma who had failed prior therapy.[22] In addition, an objective response rate of near 20% was observed in non-small cell carcinoma patients.[22–24] Pembrolizumab has shown an overall response rate of over 40% in patients with melanoma and over 20% in patients with NSCLC. Importantly, responses have been of long duration and both MK- 3475 and nivolumab are generally well tolerated.

Data from early phase clinical studies with pembrolizumab (> 700 patients) demonstrate that pembrolizumab has been generally been well tolerated at doses up to 10 mg/kg once every two to three weeks without dose-limiting toxicities. The adverse event profile of pembrolizumab in a large phase II trial in patients with metastatic melanoma is detailed in Table 1 below.[25]

Table 1 Drug-Related Adverse Events with Pembrolizumab in Patients with Melanoma

Drug-Related Event	All Grades (n=135) *number (percent)*	Grade 3 or 4 (n=135) *number (percent)*
Any	107 (79)	17 (13)
Hypothyroidism	11 (8)	1 (1)
Gastrointestinal disorder		
Diarrhea	27 (20)	1 (1)
Nausea	13 (10)	0
Abdominal pain	7 (5)	1
Generalized symptom		
Fatigue	41 (30)	2 (1)
Mylagia	16 (12)	0
Headache	14 (10)	0
Asthenia	13 (10)	0
Pyrexia	10 (7)	0
Chills	9 (7)	0
Decreased appetite	6 (4)	1 (1)
Increase in aminotransferase level		
AST	13 (10)	2 (1)
ALT	11 (8)	0
Renal failure	3 (2)	2 (1)
Respiratory disorder		
Cough	11 (8)	0
Dyspnea	6 (4)	0
Pneumonitis	6 (4)	0
Skin disorder		
Rash	28 (21)	3 (2)
Pruritis	28 (21)	1 (1)
Vitiligo	12 (9)	0

Drug related adverse events occurring in at least 5 patients or drug-related grade 3 or 4 adverse events that occurred in at least 2 patients from[25]

1.8 Inhibiting PD-1/PD-L1 signaling is associated with clinical activity in metastatic urothelial cancer.

Recently, proof of concept for targeting PD-1/PD-L1 in patients with metastatic urothelial cancer has been established. Powles et al demonstrated that in 30 patients with PD-L1-expressing (by immunohistochemistry) metastatic urothelial cancer refractory to standard chemotherapy treated with the anti-PDL1 antibody, MPDL3280A, 43% achieved an objective response.[26] Plimack et al reported the preliminary results of the urothelial cancer expansion cohort of KEYNOTE-012, a Phase Ib Multi-Cohort Study of MK3475 in Patients with PD-L1+ Advanced Solid Tumors. Among 33 chemotherapy-refractory patients treated with pembrolizumab 10 mg/kg every 2 weeks, 24% achieved an objective response including several durable responses.[27] In a phase 3 trial of pembrolizumab versus standard chemotherapy in patients with metastatic urothelial cancer progressing despite platinum-

based regimens, pembrolizumab was associated with a significant improvement in overall survival leading to approval by the US FDA for this indication.[28]

1.9 Rationale for the proposed study

A randomized phase II study of pembrolizumab versus placebo as maintenance therapy after first-line treatment of metastatic urothelial cancer is supported by the following:

1. Metastatic urothelial cancer is a chemosensitive disease though response durations are generally short-lived.
2. Bladder (urothelial) cancer is an immunogenic malignancy but patients with bladder cancer exhibit tumor-associated immune tolerance.
3. PD-L1 expression in bladder (urothelial) cancer correlates with stage and grade and is of prognostic significance.
4. PD-1/PD-L1 blockade may overcome tumor-associated immune tolerance, has shown antitumor effects in preclinical models of bladder cancer, and has shown preliminary evidence of striking anticancer activity in patients with bladder cancer.
5. Administration of chemotherapy prior to immune checkpoint blockade may augment the effects of immunotherapy, due to "auto-vaccination" and depletion of tumor-promoting cellular subsets (e.g. myeloid-derived suppressor cells).
6. Switch maintenance with checkpoint blockade may build on the responses achieved with cytotoxic chemotherapy alone to induce durable disease control and serve as a platform for curative therapy.

1.10 Rationale for Dose Selection/Regimen

In KN001, two randomized cohort evaluations of melanoma subjects receiving pembrolizumab at a dose of 2 mg/kg versus 10 mg/kg Q3W have been completed, while one randomized cohort evaluation of 10 mg/kg Q3W versus 10 mg/kg Q2W is ongoing. The clinical efficacy and safety data demonstrate a lack of clinically important differences in efficacy response or safety profile at these doses. For example, in Cohort B2, advanced melanoma subjects who had received prior ipilimumab therapy were randomized to receive pembrolizumab at 2 mg/kg versus 10 mg/kg Q3W, with an observed ORR was 26% (21/81) in the 2 mg/kg group and 26% (25/79) in the 10 mg/kg group (FAS). The proportion of subjects with drug-related AE, grade 3-5 drug-related AE, serious drug-related AE, death or discontinuation due to an AE was comparable between groups or lower in the 10 mg/kg group.

In Cohort B3 of KN001, advanced melanoma subjects (irrespective of prior ipilimumab therapy) were randomized to receive pembrolizumab at 10 mg/kg Q2W versus 10 mg/kg Q3W. The ORR was 30.9% (38/123) in the 10mg/kg Q2W group and 24.8% (30/121) in the 10 mg/kg Q3W group (ASaT). The proportion of subjects with drug-related AE, grade 3-5 drug-related AE, serious drug-related AE, death or discontinuation due to an AE was comparable between groups.

PK data analysis of pembrolizumab administered Q2W and Q3W showed slow systemic clearance, limited volume of distribution, and a long half-life (refer to IB).

Pharmacodynamic data (IL-2 release assay) suggested that peripheral target engagement is durable (>21 days), thus supporting a Q3W dosing schedule.

A population pharmacokinetic analysis has been performed using serum concentration time data from 476 subjects. Within the resulting population PK model, clearance and volume parameters of pembrolizumab were found to be dependent on body weight. The relationship between clearance and body weight, with an allometric exponent of 0.59, is within the range observed for other antibodies and would support both body weight normalized dosing or a fixed dose across all body weights. Pembrolizumab has been found to have a wide therapeutic range based on the melanoma indication. The differences in exposure for a 200 mg fixed dose regimen relative to a 2 mg/kg Q3W body weight based regimen are anticipated to remain well within the established exposure margins of 0.5 – 5.0 for pembrolizumab in the melanoma indication. The exposure margins are based on the notion of similar efficacy and safety in melanoma at 10 mg/kg Q3W versus the dose regimen of 2 mg/kg Q3W (i.e. 5-fold higher dose and exposure). The population PK evaluation revealed that there was no significant impact of tumor burden on exposure. In addition, exposure was similar between the NSCLC and melanoma indications. Therefore, there are no anticipated changes in exposure between different indication settings.

In conclusion, the above data indicates that the 200 mg Q3W fixed dose regimen planned to be used in this trial is likely similar, with regard to efficacy and tolerability, to the 10 mg/kg Q2W dose regimen used in KN012, and supports its use in this study. No dose reduction is allowed for pembrolizumab in this study.

1.11 Rationale for Endpoints

In a pooled landmark analysis of patients with metastatic bladder (urothelial) cancer treated with cisplatin-based chemotherapy on a series of phase 2 and 3 trials, we have previously demonstrated that progression-free survival and overall survival are highly correlated.[29] For example, the median overall survival for patients who had progressed at 9 months was 5.7 months compared with 21.4 months for those who had not progressed ($p<0.0001$). Using the Fleischer model, the estimated correlation between progression-free survival and overall survival was 0.86 (bootstrap standard error 0.001, 95% CI 0.82, 0.90). This finding was externally validated in an independent cohort. These findings support the use of progression-free survival as a practical, and clinically relevant, primary endpoint for the current study.

1.12 Rationale for Not Limiting Enrollment to Patients with PD-L1 Positive Tumors

Emerging data suggest that patients with PD-L1 positive tumors are more likely to respond to treatment targeting the PD-L1/PD-1 signaling axis. However, this has not been uniformly observed, likely due to various assays, tumor tissue (archival primary tumor versus post-systemic therapy metastatic tissue), and cut-points used to establish “positivity” based on this immunohistochemical assay. Furthermore, patients with “PD-L1 negative” tumors have experienced responses to treatment. Therefore, in the current study, enrollment will not be limited to patients with PD-L1 expressing tumors. However, the outcomes in PD-L1 “positive” and “negative” patients will be analyzed as a secondary endpoint.

1.13 Rationale for Modification of the Analysis Plan and Sample Size

During the conduct of the current study, five PD-1/PD-L1 antibodies have been approved by the US FDA for the treatment of patients with metastatic urothelial cancer progressing despite prior platinum-based chemotherapy and two PD-1/PD-L1 antibodies have been approved as first-line treatment for cisplatin-ineligible patients with metastatic urothelial cancer. Notably, pembrolizumab has been approved in both of these settings. The commercial availability of immune checkpoint inhibitors in the first-line and second-line settings, coupled with the large number of studies seeking to integrate these therapies earlier in the course of treatment (i.e., adjuvant setting or in combination with chemotherapy as first-line treatment for metastatic disease) has dramatically changed the treatment landscape and undoubtedly impacted enrollment. Further, results from several studies across tumor types exploring PD-1/PD-L1 inhibitors have revealed that while improvements in progression-free survival likely occur, such improvements are often not apparent using traditional survival analysis approaches due to "delayed separation of the curves" highlighting the need for novel analytic approaches.[30] To address both the slower than anticipated accrual to this randomized phase II study, and the need to develop approaches that better capture the potential benefits of immune checkpoint inhibitors particularly in the setting of progression-free survival endpoints, we have developed a novel approach as described in the Statistical Considerations (section 12).

2 STUDY OBJECTIVES

2.1 Primary Objective

The primary objective will be to determine the progression-free survival (PFS) as per immune-related RECIST (irRECIST) among subjects with metastatic urothelial cancer (mUC) treated with pembrolizumab versus placebo as maintenance therapy after up to 8 cycles of first-line chemotherapy.

2.2 Secondary Objectives

- Determine the 6-month PFS as per irRECIST
- Determine the 6-month PFS as per irRECIST among the subsets of subjects with PD-L1 positive and PD-L1 negative tumors treated with pembrolizumab versus placebo.
- Determine the PFS as per irRECIST among the subsets of subjects with PD-L1 positive and PD-L1 negative tumors treated with pembrolizumab versus placebo
- Determine the PFS as per RECIST 1.1 among subjects treated with pembrolizumab versus placebo
- Determine the objective response rate (ORR) by irRECIST and RECIST 1.1 in subjects on maintenance pembrolizumab versus placebo with measurable disease
- Determine the ORR by irRECIST and RECIST 1.1 in subjects receiving pembrolizumab after progressing on placebo
- Determine overall survival (OS) in subjects treated with pembrolizumab versus placebo
- Determine the hazard ratios (HRs) with respect to both PFS and OS comparing subjects treated with pembrolizumab versus placebo
- Determine the restricted mean survival time (RMST) in subjects treated with pembrolizumab versus placebo

- Determine durations of response in subjects treated with pembrolizumab versus placebo
- Determine the safety of pembrolizumab administration in this patient population

2.3 Exploratory Objectives

- Determine the PFS and 6mPFS rate among subjects without visceral metastatic disease randomized to pembrolizumab versus placebo
- Compare PD-L1 expression in primary tumor tissue and metastatic post first-line chemotherapy tumor tissue in a subgroup of subjects.
- Correlate immune infiltrates in tumor tissue with response rate, progression-free survival, and overall survival in subjects receiving pembrolizumab versus placebo
- Determine the repertoire of humoral responses and correlate with response rate, progression-free survival, and overall survival
- Determine the induction of T cell responses and correlate with response rate, progression-free survival, and overall survival
- Correlate genomic alterations with response rate, progression-free survival, and overall survival
- Correlate tobacco history with PFS in subjects receiving pembrolizumab versus placebo

3 ELIGIBILITY CRITERIA

3.1 Inclusion Criteria

1. Written informed consent and HIPAA authorization for release of personal health information. **NOTE:** HIPAA authorization may be included in the informed consent or obtained separately.
2. Age ≥ 18 years at the time of consent.
3. ECOG Performance Status (PS) of ≤ 1 within fourteen days of registration for protocol therapy.
4. Histological or cytological evidence of urothelial cancer of the bladder, urethra, ureter, or renal pelvis. Differentiation with variant histologies (e.g., squamous cell differentiated) will be permitted provided that the predominant histology is urothelial carcinoma.
5. Metastatic and/or unresectable (cT4b) disease
6. Must have achieved an objective response (CR/PR) or stable disease (SD) upon completion of scheduled treatment.
7. Subjects may have had up to 8 cycles of standard first-line platinum-based chemotherapy for mUC (e.g., as per NCCN guidelines). Able to commence study treatment within 2 to 6 weeks of receiving last dose of first-line chemotherapy.
8. All subjects must have adequate archival tissue available prior to registration (i.e., at least 20 unstained slides or paraffin block). If acceptable archival tissue is not available, the subject must be willing to consent to providing a core or excisional biopsy for research prior to registration for protocol therapy. If archival tissue is not available and there are no sites amenable to biopsy, enrollment must be discussed with the sponsor-investigator on a case by case basis.

9. Required laboratory values, as outlined in Table 2, must be obtained within 14 days prior to registration for protocol therapy.

Table 2 Required Lab Values

System	Lab Value
Hematological	
Absolute neutrophil count (ANC)	≥1,500 /mcL
Platelets	≥100,000 / mcL
Hemoglobin	≥8.5 g/dL
Renal	
Creatinine OR Measured or calculated [a] creatinine clearance (GFR can also be used in place of creatinine or CrCl)	≤1.5xULN OR ≥30 mL/min for subject with creatinine levels >1.5x institutional ULN
Hepatic	
Serum total bilirubin	≤ 1.5 X ULN **OR**
	Direct bilirubin ≤ ULN for subjects with total bilirubin levels > 1.5 ULN
AST (SGOT) and ALT (SGPT)	≤ 2.5 X ULN **OR** ≤ 5 X ULN for subjects with liver metastases
Coagulation	
International Normalized Ratio (INR) or Prothrombin Time (PT) Activated Partial Thromboplastin Time (aPTT)	≤1.5 X ULN unless subject is receiving anticoagulant therapy. If subject on anticoagulant therapy, PT or PTT must within therapeutic range of intended use of anticoagulants

[a] Creatinine clearance should be calculated per institutional standard

10. Female subjects of childbearing potential must have a negative serum pregnancy within three days prior to registration for protocol therapy
11. Sexually active, pre-menopausal women of childbearing potential must be willing to use an adequate method of contraception or be surgically sterile, or abstain from heterosexual activity for the course of the study through 120 days after the last dose of study drug. Subjects of childbearing potential are those who have not been surgically sterilized or have not been free from menses for > one year.
12. Male subjects of childbearing potential must agree to use an adequate method of contraception starting with the first dose of study drug through 120 days after the last dose of study drug.

3.2 Exclusion Criteria

1. More than one line of prior chemotherapy for metastatic or locally advanced disease with the following exception:
   - prior neoadjuvant/adjuvant chemotherapy will not count as line of therapy if completed greater than 12 months prior to initiation of chemotherapy regimen for metastatic or unresectable disease.
2. Current or past participation in a study of an investigational agent or using an investigational device within four weeks of registration for protocol therapy.

3. Diagnosis of immunodeficiency or is receiving treatment with systemic steroid therapy or any other form of immunosuppressive therapy within seven days prior to registration for protocol therapy.
4. Prior chemotherapy, targeted small molecule therapy, or radiation therapy within two weeks prior to registration for protocol therapy. Note: If the subjects have undergone major surgery, they must have recovered adequately from the toxicity and/or complications from the intervention prior to starting protocol therapy.
5. Known additional malignancy that is progressing or requires active treatment. Exceptions include basal cell carcinoma of the skin, squamous cell carcinoma of the skin, or in situ cervical cancer that has undergone potentially curative therapy.
6. Known active central nervous system (CNS) metastases and/or carcinomatous meningitis. Subjects with previously treated brain metastases may participate provided they are stable (without evidence of progression by imaging for at least four weeks prior to registration for protocol therapy and any neurologic symptoms have returned to baseline), have no evidence of new or enlarging brain metastases, and are not using steroids for at least seven days prior to registration for protocol therapy.
7. Active autoimmune disease requiring systemic treatment within the past three months or a documented history of clinically severe autoimmune disease, or a syndrome that requires systemic steroids or immunosuppressive agents. Exceptions include: subjects with vitiligo or resolved childhood asthma/atopy. Subjects who require intermittent use of bronchodilators or local steroid injections, and subjects with hypothyroidism who are stable on hormone replacement or Sjögren's syndrome are eligible for the study.
8. Has a history of (non-infectious) pneumonitis that required steroids or current pneumonitis.
9. Active infection requiring systemic therapy.
10. History or current evidence of any condition, therapy, or laboratory abnormality that might confound the results of the trial, interfere with the subject's participation for the full duration of the trial, or is not in the best interest of the subject to participate, in the opinion of the site investigator.
11. Known psychiatric or substance abuse disorders that would interfere with cooperation with the requirements of the trial.
12. Pregnant or breastfeeding, or expecting to conceive or father children within the projected duration of the trial, starting with the screening period through 120 days after the last dose of protocol therapy.
13. Prior therapy with an anti-PD-1, anti-PD-L1, anti-PD-L2, anti-CD137, or anti-Cytotoxic T-lymphocyte-associated antigen-4 (CTLA-4) antibody (including ipilimumab or any other antibody or drug specifically targeting T-cell co-stimulation or checkpoint pathways). Examples include nivolumab, MPDL3280, etc.
14. Known history of Human Immunodeficiency Virus (HIV) (HIV 1/2 antibodies).
15. Known active Hepatitis B (e.g., HBsAg reactive) or Hepatitis C (e.g., HCV RNA [qualitative] is detected).
16. Receipt of a live vaccine within 30 days prior to registration for protocol therapy. (See Section 5.1.3 for an example list of live vaccines)

17. Unresolved toxicity (i.e., > Grade 1 or above baseline) due to previously administered agents. Exception includes: subjects with ≤ Grade 2 neuropathy are eligible for the study.

4 SUBJECT REGISTRATION

Sites must register all subjects through Hoosier Cancer Research Network's electronic data (EDC) capture system. A subject is considered registered to the protocol when an "on study" date has been entered into the EDC system. Randomization will occur after registering a subject in the EDC system. Subjects must begin protocol therapy within **five business days** of randomization.

4.1 Stratification

Stratification factors for randomization: Presence of visceral metastatic disease (lung, liver, or bone or other organs vs. lymph node only) at the time of initiation of first-line chemotherapy, and response to first-line chemotherapy (CR/PR vs. SD).

5 TREATMENT PLAN

5.1 Treatment Schedule/Administration

Table 3 Treatment Schedule

Arm	Drug	Dose	Frequency of administration	Route of administration	Duration
A	Placebo	NA	Every 3 weeks	Intravenous (IV) infusion	Up to 24 months
B	Pembrolizumab	200 mg	Every 3 weeks	IV infusion	Up to 24 months

Protocol therapy will be administered on Day 1 (± 3 days) of each three-week cycle. Pembrolizumab (Experimental Arm B) or placebo (Control Arm A) will be administered as a 30 minute IV infusion. Sites should make every effort to target infusion timing to be as close to 30 minutes as possible. However, given the variability of infusion pumps from site to site, a window of -five minutes and +10 minutes is permitted (i.e., infusion time is 30 minutes: -5 min/+10 min).

For Control Arm A, commercially available normal saline will be used as the placebo. No active placebo drug will be mixed with the normal saline.

Treatment will continue, in the absence of prohibitive toxicities or disease progression, for up to 24 months. Upon progression, subjects who are randomized to placebo will have an option to cross over to receive pembrolizumab treatment. See section 7.3.2. Subjects who randomize to placebo but come off study treatment due to toxicity may cross over to receive treatment with pembrolizumab provided their toxicities resolve to baseline.

Dosing interruptions are permitted in the case of medical / surgical events or logistical reasons not related to study therapy (e.g., elective surgery, unrelated medical events, patient vacation, and/or holidays). Subjects should be placed back on study therapy within 3 weeks of the scheduled interruption, unless otherwise discussed with the sponsor-investigator. The reason for interruption should be documented in the subject's study record.

5.1.1. Dose Calculations

The dose amount required to prepare the pembrolizumab infusion solution is a fixed dose (i.e., not based on the subject's weight) as per Table 3.

5.1.2. Pre-medications

No premedications are required prior to protocol therapy administration.

5.1.3. Concurrent Therapy and Dose Modifications

5.1.3.1 Concomitant Medications/Vaccinations (Allowed & Prohibited)

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

5.1.3.2 Acceptable Concomitant Medications

All treatments that the site investigator considers necessary for a subject's welfare may be administered at the discretion of the site investigator in keeping with the community standards of medical care. All concomitant medication will be recorded on the case report form (CRF) including all prescription, over-the-counter (OTC), herbal supplements, and IV medications and fluids. If changes occur during the trial period, documentation of drug dosage, frequency, route, and date may also be included on the CRF.

All concomitant medications received within 30 days before the first dose of trial treatment and 30 days after the last dose of trial treatment should be recorded. Concomitant medications administered after 30 days after the last dose of trial treatment should be recorded for SAEs and ECIs.

5.1.3.3 Prohibited Concomitant Medications

Subjects are prohibited from receiving the following therapies during the Screening and Treatment Phase (including retreatment for post-complete response relapse) of this trial:

- Antineoplastic systemic chemotherapy or biological therapy
- Immunotherapy not specified in this protocol
- Chemotherapy not specified in this protocol
- Investigational agents other than pembrolizumab
- Radiation therapy; **NOTE:** Radiation therapy to a symptomatic solitary lesion or to the

brain may be considered on an exceptional case by case basis after consultation with sponsor-investigator. The subject must have clear measurable disease outside the radiated field. Administration of palliative radiation therapy will be considered clinical progression for the purposes of determining PFS.

- Live vaccines within 30 days prior to the first dose of trial treatment and while participating in the trial. Examples of live vaccines include, but are not limited to, the following: measles, mumps, rubella, chicken pox, yellow fever, rabies, BCG, and typhoid (oral) vaccine. Seasonal influenza vaccines for injection are generally killed virus vaccines and are allowed. However, intranasal influenza vaccines (e.g. Flu - Mist®) are live attenuated vaccines, and are not allowed.
- Systemic glucocorticoids for any purpose other than to modulate symptoms from an event of clinical interest of suspected immunologic etiology. The use of physiologic doses of corticosteroids may be approved after consultation with the sponsor-investigator. **NOTE:** Inhaled steroids are allowed for management of asthma.

Subjects who, in the assessment by the site investigator, require the use of any of the aforementioned treatments for clinical management should be removed from the trial. Subjects may receive other medications that the site investigator deems to be medically necessary. The Exclusion Criteria describes other medications that are prohibited in this trial. There are no prohibited therapies during the Post-Treatment Follow-up Phase.

5.1.3.4 Dose Modification for Pembrolizumab

Serious and non-serious adverse events associated with pembrolizumab exposure may represent an immunologic etiology. These adverse events may occur shortly after the first dose or several months after the last dose of treatment. Pembrolizumab must be withheld for drug-related toxicities and severe or life-threatening AEs as per Table 4.

Table 4 Dose Modification and Toxicity Management Guidelines for Immune-Related AEs Associated with Pembrolizumab

General instructions:

1. Corticosteroid taper should be initiated upon AE improving to Grade 1 or less and continue to taper over at least 4 weeks.
2. For situations where pembrolizumab has been withheld, pembrolizumab can be resumed after AE has been reduced to Grade 1 or 0 and corticosteroid has been tapered. Pembrolizumab should be permanently discontinued if AE does not resolve within 12 weeks of last dose or corticosteroids cannot be reduced to ≤10 mg prednisone or equivalent per day within 12 weeks.
3. For severe and life-threatening irAEs, IV corticosteroid should be initiated first followed by oral steroid. Other immunosuppressive treatment should be initiated if irAEs cannot be controlled by corticosteroids.

Immune-related AEs	Toxicity grade or conditions (CTCAEv4.0)	Action taken to pembrolizumab	irAE management with corticosteroid and/or other therapies	Monitor and follow-up
Pneumonitis	Grade 2	Withhold	• Administer corticosteroids (initial dose of 1-2 mg/kg prednisone or equivalent) followed by taper	• Monitor participants for signs and symptoms of pneumonitis • Evaluate participants with suspected pneumonitis with radiographic imaging and initiate corticosteroid treatment • Add prophylactic antibiotics for opportunistic infections
	Grade 3 or 4, or recurrent Grade 2	Permanently discontinue		
Diarrhea / Colitis	Grade 2 or 3	Withhold	• Administer corticosteroids (initial dose of 1-2 mg/kg prednisone or equivalent) followed by taper	• Monitor participants for signs and symptoms of enterocolitis (ie, diarrhea, abdominal pain, blood or mucus in stool with or without fever) and of bowel perforation (ie, peritoneal signs and ileus). • Participants with ≥ Grade 2 diarrhea suspecting colitis should consider GI consultation and performing endoscopy to rule out colitis. • Participants with diarrhea/colitis should be advised to drink liberal quantities of clear fluids. If sufficient oral fluid intake is not feasible, fluid and electrolytes should be substituted via IV infusion.
	Grade 4	Permanently discontinue		

Immune-related AEs	Toxicity grade or conditions (CTCAEv4.0)	Action taken to pembrolizumab	irAE management with corticosteroid and/or other therapies	Monitor and follow-up
AST / ALT elevation or Increased bilirubin	Grade 2	Withhold	• Administer corticosteroids (initial dose of 0.5- 1 mg/kg prednisone or equivalent) followed by taper	• Monitor with liver function tests (consider weekly or more frequently until liver enzyme value returned to baseline or is stable
	Grade 3 or 4	Permanently discontinue	• Administer corticosteroids (initial dose of 1-2 mg/kg prednisone or equivalent) followed by taper	
Type 1 diabetes mellitus (T1DM) or Hyperglycemia	Newly onset T1DM or Grade 3 or 4 hyperglycemia associated with evidence of β-cell failure	Withhold	• Initiate insulin replacement therapy for participants with T1DM • Administer anti-hyperglycemic in participants with hyperglycemia	• Monitor participants for hyperglycemia or other signs and symptoms of diabetes.
Hypophysitis	Grade 2	Withhold	• Administer corticosteroids and initiate hormonal replacements as clinically indicated.	• Monitor for signs and symptoms of hypophysitis (including hypopituitarism and adrenal insufficiency)
	Grade 3 or 4	Withhold or permanently discontinue[1]		
Hyperthyroidism	Grade 2	Continue	• Treat with non-selective beta-blockers (eg, propranolol) or thionamides as appropriate	• Monitor for signs and symptoms of thyroid disorders.
	Grade 3 or 4	Withhold or permanently discontinue[1]		
Hypothyroidism	Grade 2-4	Continue	• Initiate thyroid replacement hormones (eg, levothyroxine or liothyroinine) per standard of care	• Monitor for signs and symptoms of thyroid disorders.
Nephritis and Renal dysfunction	Grade 2	Withhold	• Administer corticosteroids (prednisone 1-2 mg/kg or equivalent) followed by taper.	• Monitor changes of renal function
	Grade 3 or 4	Permanently discontinue		

Immune-related AEs	Toxicity grade or conditions (CTCAEv4.0)	Action taken to pembrolizumab	irAE management with corticosteroid and/or other therapies	Monitor and follow-up
Myocarditis	Grade 1 or 2	Withhold	• Based on severity of AE administer corticosteroids	• Ensure adequate evaluation to confirm etiology and/or exclude other causes
	Grade 3 or 4	Permanently discontinue		
All other immune-related AEs	Intolerable/ persistent Grade 2	Withhold	• Based on type and severity of AE administer corticosteroids	• Ensure adequate evaluation to confirm etiology and/or exclude other causes
	Grade 3	Withhold or discontinue based on the type of event. Events that require discontinuation include and not limited to: Gullain-Barre Syndrome, encephalitis		
	Grade 4 or recurrent Grade 3	Permanently discontinue		

1. Withhold or permanently discontinue pembrolizumab is at the discretion of the investigator or treating physician.

NOTE: For participants with Grade 3 or 4 immune-related endocrinopathy where withhold of pembrolizumab is required, pembrolizumab may be resumed when AE resolves to ≤ Grade 2 and is controlled with hormonal replacement therapy or achieved metabolic control (in case of T1DM).

5.1.3.5 Timing of Dose Administration

Trial treatment of pembrolizumab may be administered up to 3 days before or after the scheduled Day 1 of each cycle due to administrative reasons (up to 5 days after randomization is permitted).

5.2 Rescue Medications & Supportive Care

5.2.1 Supportive Care Guidelines for Pembrolizumab

Subjects should receive appropriate supportive care measures as deemed necessary by the site investigator. Suggested supportive care measures for the management of adverse events with potential immunologic etiology are outlined below and in greater detail in. Where appropriate, these guidelines include the use of oral or intravenous treatment with corticosteroids as well as additional anti-inflammatory agents if symptoms do not improve with administration of corticosteroids. Note that several courses of steroid tapering may be necessary as symptoms may worsen when the steroid dose is decreased. For each disorder, attempts should be made to rule out other causes such as metastatic disease or bacterial or viral infection, which might require additional supportive care. The treatment guidelines are intended to be applied when the site investigator determines the events to be related to pembrolizumab.

Pneumonitis:

- For Grade 2 events, treat with systemic corticosteroids. When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks.
- For Grade 3-4 events, immediately treat with intravenous steroids. Administer additional anti-inflammatory measures, as needed.
- Add prophylactic antibiotics for opportunistic infections in the case of prolonged steroid administration.

Diarrhea/Colitis:

Subjects should be carefully monitored for signs and symptoms of enterocolitis (such as diarrhea, abdominal pain, blood or mucus in stool, with or without fever) and of bowel perforation (such as peritoneal signs and ileus).

- All subjects who experience diarrhea/colitis should be advised to drink liberal quantities of clear fluids. If sufficient oral fluid intake is not feasible, fluid and electrolytes should be substituted via IV infusion. For Grade 2 or higher diarrhea, consider GI consultation and endoscopy to confirm or rule out colitis.
- For Grade 2 diarrhea/colitis that persists greater than 3 days, administer oral corticosteroids.
- For Grade 3 or 4 diarrhea/colitis that persists > 1 week, treat with intravenous steroids followed by high dose oral steroids.
- When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks.

Type 1 diabetes mellitus (if new onset, including diabetic ketoacidosis [DKA]) **or ≥ Grade 3 Hyperglycemia, if associated with ketosis (ketonuria) or metabolic acidosis (DKA)**

- For T1DM or Grade 3-4 Hyperglycemia
  - Insulin replacement therapy is recommended for Type I diabetes mellitus and for Grade 3-4 hyperglycemia associated with metabolic acidosis or ketonuria.
  - Evaluate subjects with serum glucose and a metabolic panel, urine ketones, glycosylated hemoglobin, and C-peptide.

Hypophysitis:

- For Grade 2 events, treat with corticosteroids. When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks. Replacement of appropriate hormones may be required as the steroid dose is tapered.
- For Grade 3-4 events, treat with an initial dose of IV corticosteroids followed by oral corticosteroids. When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks. Replacement of appropriate hormones may be required as the steroid dose is tapered.

Hyperthyroidism or Hypothyroidism:

Thyroid disorders can occur at any time during treatment. Monitor subjects for changes in thyroid function (at the start of treatment, periodically during treatment, and as indicated based on clinical evaluation) and for clinical signs and symptoms of thyroid disorders.

- Grade 2 hyperthyroidism events (and Grade 2-4 hypothyroidism):
  - In hyperthyroidism, non-selective beta-blockers (e.g. propranolol) are suggested as initial therapy.
  - In hypothyroidism, thyroid hormone replacement therapy, with levothyroxine or liothyroinine, is indicated per standard of care.
- Grade 3-4 hyperthyroidism
  - Treat with an initial dose of IV corticosteroid followed by oral corticosteroids. When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks. Replacement of appropriate hormones may be required as the steroid dose is tapered.

Hepatic:

- For Grade 2 events, monitor liver function tests more frequently until returned to baseline values (consider weekly).
  - Treat with IV or oral corticosteroids
- For Grade 3-4 events, treat with intravenous corticosteroids for 24 to 48 hours.
- When symptoms improve to Grade 1 or less, a steroid taper should be started and continued over no less than 4 weeks.

Renal Failure or Nephritis:

- For Grade 2 events, treat with corticosteroids.
- For Grade 3-4 events, treat with systemic corticosteroids.
- When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks.

Management of Infusion Reactions: Signs and symptoms usually develop during or shortly after drug infusion and generally resolve completely within 24 hours of completion of infusion. Appropriate resuscitation equipment should be available in the room and a physician readily available during the period of drug administration.

Table 5 shows treatment guidelines for subjects who experience an infusion reaction associated with administration of pembrolizumab (MK-3475).

Table 5 Infusion Reaction Treatment Guidelines

NCI CTCAE Grade	Treatment	Premedication at subsequent dosing
Grade 1 Mild reaction; infusion interruption not indicated; intervention not indicated	Increase monitoring of vital signs as medically indicated until the subject is deemed medically stable in the opinion of the site investigator.	None
Grade 2 Requires infusion interruption but responds promptly to symptomatic treatment (e.g., antihistamines, NSAIDS, narcotics, IV fluids); prophylactic medications indicated for < =24 hrs	**Stop Infusion and monitor symptoms.** Additional appropriate medical therapy may include but is not limited to: IV fluids Antihistamines NSAIDS Acetaminophen Narcotics Increase monitoring of vital signs as medically indicated until the subject is deemed medically stable in the opinion of the site investigator. If symptoms resolve within one hour of stopping drug infusion, the infusion may be restarted at 50% of the original infusion rate (e.g., from 100 mL/hr to 50 mL/hr). Otherwise dosing will be held until symptoms resolve and the subject should be premedicated for the next scheduled dose. **Subjects who develop Grade 2 toxicity despite adequate premedication should be permanently discontinued from further trial treatment administration.**	Subject may be premedicated 1.5h (± 30 minutes) prior to infusion of pembrolizumab with: Diphenhydramine 50 mg po (or equivalent dose of antihistamine). Acetaminophen 500-1000 mg po (or equivalent dose of antipyretic).
Grades 3 or 4 Grade 3: Prolonged (i.e., not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for other clinical sequelae (e.g., renal impairment, pulmonary infiltrates)	**Stop Infusion.** Additional appropriate medical therapy may include but is not limited to: IV fluids Antihistamines NSAIDS Acetaminophen Narcotics Oxygen Pressors Corticosteroids Epinephrine	No subsequent dosing

NCI CTCAE Grade	Treatment	Premedication at subsequent dosing
Grade 4: Life-threatening; pressor or ventilatory support indicated	Increase monitoring of vital signs as medically indicated until the subject is deemed medically stable in the opinion of the site investigator. Hospitalization may be indicated. **Subject is permanently discontinued from further trial treatment administration.**	

5.3 Diet/Activity/Other Considerations

5.3.1 Diet

Subjects should maintain a normal diet unless modifications are required to manage an AE such as diarrhea, nausea or vomiting.

5.3.2 Contraception

Pembrolizumab may have adverse effects on a fetus in utero. Furthermore, it is not known if pembrolizumab has transient adverse effects on the composition of sperm. Therefore, non-pregnant, non-breast-feeding women may only be enrolled if they are willing to use an adequate form of contraception or are considered highly unlikely to conceive. Highly unlikely to conceive is defined as 1) surgically sterilized, or 2) postmenopausal (a woman who is ≥45 years of age and has not had menses for greater than 1 year will be considered postmenopausal), or 3) not heterosexually active for the duration of the study. The two birth control methods can be either two barrier methods or a barrier method plus a hormonal method to prevent pregnancy. Subjects should start using birth control from study Visit 1 throughout the study period up to 120 days after the last dose of study therapy.

The following are considered adequate barrier methods of contraception: diaphragm, condom (by the partner), copper intrauterine device, sponge, or spermicide as per local regulations or guidelines. Appropriate hormonal contraceptives will include any registered and marketed contraceptive agent that contains an estrogen and/or a progestational agent (including oral, subcutaneous, intrauterine, or intramuscular agents).

Subjects should be informed that taking the study medication may involve unknown risks to the fetus (unborn baby) if pregnancy were to occur during the study. In order to participate in the study they must adhere to the contraception requirement (described above) for the duration of the study and during the follow-up period. If there is any question that a subject will not reliably comply with the requirements for contraception, that subject should not be entered into the study.

5.3.3 Use in Pregnancy

If a subject inadvertently becomes pregnant while on treatment with pembrolizumab, the subject will immediately be removed from the study. The site will contact the subject at least monthly and document the subject's status until the pregnancy has been completed or terminated. The site investigator will make every effort to obtain permission to follow the outcome of the pregnancy and report the condition of the fetus or newborn to HCRN. If a male subject impregnates his female partner the study personnel at the site must be informed immediately and the pregnancy reported to HCRN and followed as described above.

5.3.4 Use in Nursing Women

It is unknown whether pembrolizumab is excreted in human milk. Since many drugs are excreted in human milk, and because of the potential for serious adverse reactions in the nursing infant, subjects who are breast-feeding are not eligible for enrollment.

6 TREATMENT DISCONTINUATION

6.1 Reasons for Discontinuing Protocol Therapy

A subject will be discontinued from protocol therapy under the following circumstances:

- If there is evidence of progressive disease. However, subjects randomized to placebo will be eligible to cross over to pembrolizumab treatment at the time of progression.
- If the site investigator thinks a change of therapy would be in the best interest of the subject.
- If the drug(s) exhibit(s) an unacceptable adverse event.
- If a subject becomes pregnant or is unwilling to use appropriate birth control techniques as outlined in the inclusion criteria.
- If there is a treatment interruption for greater than 12 weeks due to treatment related adverse event.
- Subjects can stop participating at any time. However, if they decide to stop participating in the study, subjects will continue to be followed for disease progression and survival.
- Twenty-four months of uninterrupted protocol therapy and no evidence of progressive disease.

6.2 Reasons for Withdrawal from Study

- Subject withdraws consent for participation
- Termination of the study
- Lost to follow-up
- Death

7 STUDY SCHEDULE OF EVENTS

	Screening		RANDOMIZATION	On Treatment Cycle = 3 weeks (up to 24 months)	Progression/Unblinding EOT[15]	Cross-over to pembrolizumab	Follow-up
	-28 days	-14 days		Cycles 1+ Day 1 (±3)	30 days (±7) after last dose	Cycle 1+ Day 1 (±3)	
REQUIRED ASSESSMENTS							
Eligibility evaluation (review of inclusion and exclusion criteria)[1]	X	X			X		
Medical history		X					
Physical examination		X		X	X	X	
Vitals and ECOG performance status[2]		X		X	X	X	
Charlson Comorbidity Index		X					
Smoking History Questionnaire[3]		X					
AEs & concomitant medications		X		X	X	X	
LABORATORY ASSESSMENTS							
CMP[4]		X		X[10]	X	X[10]	
CBC[4]		X		X[10]	X	X[10]	
PT/INR and aPTT[5]		X				X[5]	
Thyroid Function (TSH, T3 and T4)[6]		X		X[6]		X[6]	
Serum pregnancy test[7]		X[7]					
DISEASE ASSESSMENT							
CT or MRI of chest, abdomen, and pelvis	X[12]			X[11]	[X][12]	X[11]	[X][13]
TREATMENT EXPOSURE							
pembrolizumab or placebo (IV)				X		X	
CORRELATIVE STUDIES							
Archival tumor tissue for research[8]	X						
Tumor Biopsy if archival tissue not available[8]	X						
Tumor Biopsy for sub-study analysis[8]	X						
Blood samples for research[9]				X	X	X	
FOLLOW-UP							
For progression, start date of additional cancer treatment, and survival[14]							X[14]

1. Subjects should undergo informed consent prior to any research specific testing being performed. Subjects randomized to Arm A (placebo) who discontinue treatment due to progression or unacceptable toxicity will be eligible to cross over to pembrolizumab provided eligibility outlined in section 3 is met. (**NOTE:** inclusion criteria #6 regarding initiation of study treatment within 2 to 6 weeks of completing first line chemotherapy only applies to initial randomization to placebo). Cross over treatment should be initiated within 4 weeks of confirming eligibility. Subjects initiating treatment with pembrolizumab from placebo will follow the same schedule outlined in the calendar above and receive up to 24 months of treatment unless progression or unacceptable toxicity is experienced.
2. Vital signs (blood pressure, weight [kg] and height [cm] SCREENING ONLY and ECOG performance status.
3. Smoking Questionnaire in Appendix A
4. CMP includes: serum chemistries (creatinine, glucose, total protein, blood urea nitrogen [BUN], total carbon dioxide [CO2], albumin, total bilirubin, alkaline phosphatase, and aspartate transaminase [AST] and alanine transaminase [ALT]) and electrolytes (total calcium, chloride, potassium, sodium). CBC includes: platelets, ANC & HGB.
5. Repeat PT/INR and aPTT tests for subjects being screened for eligibility to cross over to pembrolizumab.
6. TSH, T3 and T4 tests are done on Day 1 of even numbered cycles only (i.e., Cycle 2, 4, 6, etc.). For T3 and T4, free versus total is at the site investigator's discretion
7. Obtain a negative serum pregnancy test for females of childbearing potential within three days of registration for protocol therapy.
8. Request from all subjects, **archived tumor tissue** (primary or metastatic based on availability) for research. If archival tissue is unavailable, obtain an excisional or percutaneous **core biopsy** (only) for research. If no sites are amendable to biopsy, enrollment must be discussed with the sponsor-investigator on a case by case basis. **NOTE for biopsy for sub-study analysis:** If the subject has archived primary tissue available and has agreed to the optional exploratory sub-study analysis, collect archived **primary** tumor tissue at baseline, **and obtain** an excisional or percutaneous core biopsy (only) for research.
9. Blood samples for research will be collected prior to treatment on Cycle 1 Day 1, Cycle 4 Day 1, and at Progression (if subject's disease progressed) or End of Treatment (if for a reason other than progression). Samples will be obtained during the randomized portion of the trial and at these same time points for subjects who cross over from placebo to unblinded treatment with pembrolizumab. Subjects crossing over from placebo to unblinded treatment with pembrolizumab will have their initial progression samples count as their cross over Cycle 1 Day 1 samples. Blood samples are not to be shipped so that they are received on a weekend or holiday. Samples leftover after initial protocol testing is complete may be stored for unspecified future cancer related research. Consent will be obtained from subjects.
10. Cycle 1 Day 1 only, required tests do not need to be repeated if done within seven days prior.
11. Restaging CT or MRI of the chest, abdomen, and pelvis is performed after every four cycles of treatment (i.e., approximately every 12 weeks). Make every effort to perform the same imaging modality throughout the study. After the first documentation of progression per RECIST 1.1, if the subject is clinically stable, confirmatory scans should be performed 4-6 weeks later (see Section 7.6 for details).
12. Repeat imaging tests if it has been > 28 days since the last radiological assessment.
13. Subjects who discontinue treatment without evidence of progression will be followed with imaging studies performed every three months (± 7 days), or until new anticancer treatment is initiated. Make every effort to perform the same imaging modality throughout the follow up period.
14. After the EOT visit, make every possible attempt to contact the subject or family to information on start date of additional anticancer treatment and survival, every three months (±7 days) during the first two years, every six months (±7 days) during years 3-5, and annually (±2 weeks) thereafter.

15. Treatment will be discontinued if evidence of disease progression, unacceptable toxicity, subject withdraws or after 24 months, whichever comes first. Please see Section 7.3.2 for unblinding and Section 7.3.3 for cross over information.

Table 6 Schedule for correlative blood sample collections*

Time point	**Correlative blood samples**
Pre-Treatment Cycle 1 Day 1	1 red top tube (10 ml total) 1 Tempus tubes (3 ml total) 6 ACD tubes (51 ml total)
Pre-Treatment Cycle 4 Day 1	1 red top tube (10 ml total) 1 Tempus tubes (3 ml total) 6 ACD tubes (51 ml total)
Time of progression**	1 red top tube (10 ml total) 1 Tempus tubes (3 ml total) 6 ACD tubes (51 ml total)
End of treatment***	1 red top tube (10 ml total) 1 Tempus tubes (3 ml total) 6 ACD tubes (51 ml total)
Cross-over Cycle 1 Day 1**	1 red top tube (10 ml total) 1 Tempus tubes (3 ml total) 6 ACD tubes (51 ml total)
Cross-over Cycle 4 Day 1	1 red top tube (10 ml total) 1 Tempus tubes (3 ml total) 6 ACD tubes (51 ml total)
Cross-over Time of progression	1 red top tube (10 ml total) 1 Tempus tubes (3 ml total) 6 ACD tubes (51 ml total)
End of treatment***	1 red top tube (10 ml total) 1 Tempus tubes (3 ml total) 6 ACD tubes (51 ml total)

*Samples will be obtained during the randomized portion of the trial and at these same time points for subjects who cross over from placebo to unblinded treatment with pembrolizumab

**Subjects crossing over from placebo to unblinded treatment with pembrolizumab will have their initial progression samples count as their cross over Cycle 1 Day 1 samples

***Subjects discontinuing treatment for reasons other than progression will have correlative samples drawn at the end of treatment visit.

7.1 Screening

7.1.1 Within 28 days prior to registration for protocol therapy:

- Informed consent prior to research specific testing
- Radiological assessment (CT or MRI of chest, abdomen, and pelvis) with tumor measurements
- Identification of available paraffin embedded block or adequate unstained slides of archived tumor tissue (primary or metastatic based on availability).
  - **NOTE:** if adequate archived tissue is unavailable, excisional or percutaneous core tumor biopsy is required for research purposes.
- OPTIONAL SUB-STUDY ANALYSIS: For subjects who have archival tissue from primary site, and who agree to the exploratory sub-study analysis comparing PD-L1 expression in primary tumor tissue versus metastatic post first-line chemotherapy tumor tissue, perform excisional or percutaneous core tumor biopsy for research.

7.1.2 Within 14 days prior to registration for protocol therapy unless otherwise noted:

- Eligibility evaluation (review of inclusion and exclusion criteria)
- Medical history
- Physical examination
- Vital signs including Blood pressure, Weight [kg] Height [cm] (SCREEN ONLY) and ECOG PS
- Laboratory testing:
  - Complete metabolic profile (CMP) will include: serum chemistries (creatinine, glucose, total protein, blood urea nitrogen [BUN], total carbon dioxide [CO2], albumin, total bilirubin, alkaline phosphatase, and aspartate transaminase [AST] and alanine transaminase [ALT]) and electrolytes (total calcium, chloride, potassium, sodium).
  - CBC (including platelets, ANC & HGB)
  - PT/INR and aPTT
  - TSH, T3 and T4 tests are done. For T3 and T4, free versus total is at the site investigator's discretion
  - Serum pregnancy test for female subjects of childbearing potential (within three days of registration for protocol therapy).
- Smoking History Questionnaire (Appendix A)
- Charlson Comorbidity Index assessment (See SPM for form)
- Record Adverse Events and concomitant medications

7.2 On Treatment: Day 1 of each Cycle (± 3 days) unless otherwise noted:

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

- Physical examination
- Vital signs including Blood pressure and Weight [kg] and ECOG PS
- Laboratory testing:
  - CMP will include: serum chemistries (creatinine, glucose, total protein, BUN, total CO2, albumin, total bilirubin, alkaline phosphatase, and AST and ALT) and electrolytes (total calcium, chloride, potassium, sodium)
  - CBC (including platelets, ANC & HGB)
  - TSH, T3 and T4 tests are done on Day 1 of even numbered cycles only (i.e., Cycle 2, 4, 6, etc.). For T3 and T4, free versus total is at the site investigator's discretion
  - Correlative studies: Blood sample collection (See Table 7 above for correlative sample schedule)
- Record Adverse Events and any changes to concomitant medications
- Restaging CT or MRI of the chest, abdomen, and pelvis is performed after every four cycles of treatment (i.e., approximately every 12 weeks). Make every effort to perform the same imaging modality throughout the study.
- Pembrolizumab or placebo administration (IV)

7.3 Progression/Unblinding/End of Treatment (EOT)

Treatment will be discontinued if there is evidence of disease progression or unacceptable toxicity or if the subject stops participating or withdraws from the study. After the first documentation of progression per RECIST 1.1, if the subject is clinically stable, confirmatory scans should be performed 4-6 weeks later (see Section 7.3.2 for details).

7.3.1 End of Treatment Visit: 30 days after last dose of study drug (± 7 days)

- Physical examination
- Blood pressure
- Weight [kg]
- ECOG PS
- Laboratory testing:
  - CMP will include: serum chemistries (creatinine, glucose, total protein, BUN, total CO2, albumin, total bilirubin, alkaline phosphatase, and AST and ALT) and electrolytes (total calcium, chloride, potassium, sodium)
  - CBC (including platelets, ANC & HGB)
  - Correlative studies: Blood sample collection (see Table 7 above for correlative sample schedule)
- Record Adverse Events and changes to concomitant medications
- Subjects will continue to be followed until resolution or stabilization of any treatment-related toxicities.
- Radiological assessments (only if >28 days since last assessment).

7.3.2 Unblinding

Blinding of the treatment assignment is critical to the integrity of this clinical study. There are situations, however, in which unblinding is necessary. The patient's safety takes priority over any other considerations in determining if the treatment assignment should be unblinded. Before breaking the blind of an individual patient's treatment, the site investigator should determine that the unblinded information is necessary. **The decision to unblind the treatment assignment will be discussed with the sponsor-investigator, but the site investigator always has ultimate authority for the decision to unblind.**

Situations in which unblinding is necessary include but are not limited to:

- Time of treatment discontinuation due to disease progression
- Time of treatment discontinuation due to unacceptable toxicity
- A medical event in an individual subject in which knowledge of the investigational product is critical to the subject's clinical management.

Because of the various situations that can lead to unblinding, and the potential impact of unblinding on the primary endpoint, the following approach will be utilized:

- Patients who are unblinded for toxicity and confirmed to be on pembrolizumab, but who meet criteria for continued treatment with pembrolizumab due to effective management of the toxicity as per 5.1, may continue pembrolizumab and will be followed for the primary endpoint of progression as per section 7.6.
- Patients who are unblinded for a first progression event and confirmed to be on pembrolizumab, but who are considered clinically stable and suitable by the treating investigator for ongoing treatment while awaiting confirmatory scans 4-6 weeks later as per 7.6 may continue pembrolizumab until progression is confirmed. If progression is confirmed at the follow-up scan as outlined in 7.6, the initial date of progression will be considered the progression date. If progression is not confirmed, patients may continue treatment with pembrolizumab.

7.3.3 Cross Over

Subjects receiving placebo will be eligible for cross over to treatment with pembrolizumab provided that eligibility outlined in section 3 is still met. (**NOTE**: Inclusion criteria #6 regarding initiation of study treatment within 2 to 6 weeks of completing first line chemotherapy only applies to initial randomization to placebo).

Cross over treatment should be initiated within 4 weeks of confirming eligibility. Subjects initiating treatment with pembrolizumab from placebo will follow the same schedule outlined in the study schedule of events in section 7 and receive up to 24 months of treatment unless progression or unacceptable toxicity is experienced.

Subjects initially randomized to placebo, who discontinue treatment due to unacceptable toxicity rather than progression, may be eligible for cross over to treatment with pembrolizumab provided resolution of the toxicity (or improvement to baseline), the eligibility outlined in section 3 is still met, and after discussion with the sponsor-investigator.

Subjects who cross over to pembrolizumab and discontinue treatment for any reason will follow the same study procedures as outlined above for the EOT visit.

7.4 Follow-up

Subjects who discontinue treatment without evidence of tumor progression will be followed for progression with imaging studies performed every three months (±7 days), or until new treatment is initiated. Every effort should be made to perform the same imaging modality (e.g., CT or MRI) throughout the follow-up period. The site investigator or designees will make every possible attempt every three months (±7 days), for two years from completion of protocol therapy, every six months (±7 days) for years 3-5, and annually thereafter (±2 weeks), to contact the subject or family to obtain the survival information of the subject and start date of additional anticancer treatment.

7.5 Restaging Evaluations

A restaging CT or MRI of the chest, abdomen, and pelvis will be performed after every four cycles of treatment (i.e., approximately every 12 weeks). For subjects on an increased dosing interval (every four weeks) due to pneumonitis, the frequency of restaging imaging studies should be discussed with the sponsor-investigator. Every effort should be made to perform the same imaging modality (e.g., CT or MRI) throughout the study. After the first documentation of progression per RECIST 1.1, if the subject is clinically stable, confirmatory scans should be performed 4-6 weeks later (see Section 7.6 for details).

7.6 Determination of Progression/Post-progression imaging

Immunotherapeutic agents such as pembrolizumab may produce antitumor effects by potentiating endogenous cancer-specific immune responses. The response patterns seen with such an approach may extend beyond the typical time course of responses seen with cytotoxic agents, and can manifest as a clinical response after an initial increase in tumor burden or even the appearance of new lesions.

If radiologic imaging shows PD, tumor assessment should be repeated 4-6 weeks later in order to confirm PD with the option of continuing treatment per below while awaiting radiologic confirmation of progression. If repeat imaging shows a reduction in the tumor burden compared to the initial scan demonstrating PD, treatment may be continued as per treatment calendar. If repeat imaging confirms progressive disease, subjects will be discontinued from study therapy (exception noted Table 8) and the date of the original scan documenting progression will be considered the progression date. In determining whether or not the tumor burden has increased or decreased, site investigators should consider all target lesions as well as non-target lesions.

When feasible, subjects should not be discontinued until progression is confirmed; however, the decision to continue study treatment after the 1st evidence of disease progression is at the site investigator's discretion based on the clinical status of the subject as described in Table 7.

Subjects may receive study treatment while waiting for confirmation of PD if they are clinically stable as defined by the following criteria:

- Absence of signs and symptoms indicating disease progression
- No decline in ECOG performance status
- Absence of rapid progression of disease
- Absence of progressive tumor at critical anatomical sites (e.g., cord compression) requiring urgent alternative medical intervention

Table 7: Imaging and Treatment after Site-Assessed 1st Radiologic Evidence of PD

	Clinically Stable		**Clinically Unstable**	
	Imaging	**Treatment**	**Imaging**	**Treatment**
Site based assessment indicates PD	Repeat imaging 4-6 weeks later to confirm PD	May continue study treatment at the site investigator's discretion while awaiting confirmatory scan by site	Repeat imaging 4-6 weeks later to confirm PD per physician discretion only	Discontinue treatment
Repeat scan confirms PD	No additional imaging required Exceptions as per note*	Discontinue treatment Exceptions as per note*	No additional imaging required	N/A
Repeat scan shows SD, PR or CR	Continue regularly scheduled imaging assessments	Continue study treatment at the site investigator's discretion	Continue regularly scheduled imaging assessments	May restart study treatment if condition has improved and/or clinically stable per site investigator's discretion

Following PD by RECIST 1.1, sites will assess tumor response and progression per immune-related RECIST (irRECIST) for treatment decisions in order to determine if PD is confirmed at the follow up time point ≥ 4weeks later.

If the repeat scan documents an unconfirmed progressive disease, the subject remains clinically stable, treatment may continue and imaging should shift to the per protocol frequency.

If the subject is deemed clinically unstable, repeat imaging is not required. If the subject is clinically stable and repeat imaging in ≥4 weeks confirms PD, it is recommended that the subject be discontinued from trial treatment.

***NOTE:** If progression is confirmed per irRECIST, the subject remains clinically stable and per the site investigator is achieving extraordinary clinical benefit, the site investigator may discuss with the sponsor-investigator to consider a potential exception.

7.7 End of Study

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

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

8 CRITERIA FOR DISEASE EVALUATION

For the current study, response assessments will be made both using both RECIST v1.1, and the irRECIST allowing additional comparisons among these criteria for disease response assessment. The primary endpoint (PFS at 6 months) will utilize the irRECIST for documenting progression as outlined in 7.6. The first date of progression, confirmed on the subsequent imaging study, will be considered the date of progression.

8.1 Definitions Associated with RECIST 1.1

8.1.1 Measurable disease

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

8.1.1.1 Measurable lesions

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

8.1.1.2 Non Measurable lesions

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

Note: Cystic lesions that meet the criteria for radiographically defined simple cysts should not be considered as malignant lesions (neither measurable nor non-measurable) since they are, by definition, simple cysts.

'Cystic lesions' thought to represent cystic metastases can be considered as measurable lesions, if they meet the definition of measurability described above. However, if non-cystic lesions are present in the same subject, these are preferred for selection as target lesions.

8.1.1.3 Malignant lymph nodes

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

8.1.1.4 Baseline documentation of Target lesions

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

8.1.1.5 Baseline documentation of Non-target lesions

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

8.2 Response Criteria

8.2.1 Evaluation of target lesions

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

8.2.2 Evaluation of non-target lesions

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

*Although a clear progression of "non target" lesions only is exceptional, in such circumstances, the opinion of the site physician should prevail.

8.3 Evaluation of best overall response

The best overall response is the best response recorded from the start of the treatment until disease progression/recurrence (taking as reference for PD the smallest measurements recorded since the treatment started). In general, the subject's best response assignment will depend on the achievement of both measurement and confirmation criteria.

Target Lesions	Non-Target lesion	New Lesion	Overall response
CR	CR	No	CR
CR	Non-CR/ Non-PD	No	PR
	Not evaluated	No	PR
PR	Non-CR/ Non-PD/ not evaluated	No	PR
SD	Non-CR/ Non-PD/ not evaluated	No	SD
PD	Any	Yes or No	PD
Any	PD*	Yes or No	PD
Any	Any	Yes	PD

*In exceptional circumstances, unequivocal progression in non-target lesions may be accepted as disease progression.

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

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

8.4 Definitions for Response Evaluation – RECIST 1.1

8.4.1 First documentation of response

The time between initiation of therapy and first documentation of PR or CR.

8.4.2 Confirmation of Response

To be assigned a status of complete or partial response, changes in tumor measurements must be confirmed by repeat assessments performed no less than four weeks after the criteria for response are first met.

8.4.3 Duration of Response

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

8.4.4 Duration of Overall Complete Response

The period measured from the time that measurement criteria are met for complete response until the first date that recurrent disease is objectively documented.

8.4.5 Objective response rate

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

8.4.6 Progression Free Survival

A measurement from the start of the treatment until the criteria for disease progression is met or death occurs, taking as reference the smallest measurements recorded since the treatment started.

Progression free survival will be measured from the date of initial treatment to the earliest date of disease progression, resection of measurable tumor or death for subjects who fail; and to the date of last contact for subjects who remain at risk for failure.

8.5 Immune Related RECIST (irRECIST)

PFS, ORR and duration of response per irRECIST are defined as specified for the respective endpoints using RECIST 1.1 above, with the exception that a confirmation assessment of PD (4-6 weeks after the initial PD assessment) is required for subjects who remain on treatment following a documented PD per RECIST 1.1 (as detailed in section 7.6). The first date of progression, confirmed on the subsequent imaging study, will be considered the date of progression. Subjects who discontinue treatment following a documented PD assessment per RECIST 1.1 will be counted as having disease progression on the date of the documented PD assessment.

9 BIOLOGICAL SPECIMEN PARAMETERS FOR CORRELATIVES

9.1 Source of Study Specimens

Correlative studies will be performed using peripheral blood samples and serum samples obtained at baseline and during protocol treatment (as outlined in Section 7). All subjects are required to have archival tumor tissue (primary or metastatic based on availability) identified at screening.

If adequate archival tumor tissue is unavailable at registration, a mandatory excisional or percutaneous core biopsy for research is required. If archival tissue is not available and there are no sites amenable to biopsy, enrollment must be discussed with the sponsor-investigator on a case by case basis.

For subjects agreeing to the OPTIONAL exploratory sub-study analysis comparing PD-L1 expression in primary tumor tissue versus metastatic post first-line chemotherapy tumor tissue, archived primary tumor tissue must be available. Once availability of this tumor tissue is confirmed, an excisional or percutaneous core metastatic tumor biopsy for research will be collected prior to registration and only after eligibility criteria are verified.

9.2 Correlative studies

The immune cell infiltrate in tumor specimens will be correlated with the response rate, progression-free survival, and overall survival for subjects randomized to placebo versus pembrolizumab. The systemic immunomodulatory activity of pembrolizumab will be measured by the functional and phenotypic characterization of peripheral immune cells and soluble factors.

9.2.1 PD-L1 expression in tumor tissue

All subjects will have unstained slides available for submission for PD-L1 expression. Specimens will be analyzed by a third party laboratory, as identified by Merck, for determination of PD-L1 status using an analytically validated immunohistochemical assay.

9.2.2 Immune infiltrate in tumor tissue

Several studies have demonstrated that the presence of tumor infiltrating lymphocytes in primary tumor specimens, including bladder cancer specimens, correlate with improved long term patient outcomes.[4] Among the most powerful, yet elegantly simplistic, approach to immune-classification is the "Immunoscore" developed by Galon and colleagues. The Immunoscore utilizes two simple immunohistochemical stains (CD3 and CD8), assessed in two locations (tumor core and invasive margin), coupled with digital pathology to score the degree of T cell infiltration (as shown in the Figure).[31–33] The Immunoscore is currently being harmonized in a Society for Immunotherapy of Cancer-led effort involving 23 centers from 17 countries to become the standard approach to characterizing tumor-infiltrating lymphocytes.[34]

Sections from archival tumor tissue will be incubated with monoclonal antibodies against immune markers such as CD3, CD8, and other potential biomarkers.

9.2.3 Genomic alterations in tumor tissue and circulating DNA and RNA

The precise mechanism of action leading to tumor regression in response to treatment with immune checkpoint blockade is not fully understood. There is evidence that these agents may unmask the endogenous adaptive response to specific tumor antigens.[35–39] However, little is known about the identity of the tumor antigens that function as the targets of T cells activated by immune checkpoint blockade. Such knowledge may be critical to optimizing use of existing immunotherapies. Emerging evidence, both in model systems and in subjects, suggests that mutation-derived tumor antigens may be predominate in this regard.[40–43] We will use genomic sequencing strategies in tumor tissue (DNA and RNA) and circulating DNA and RNA to correlate response rate, progression-free survival, and overall survival with mutational burden and with specific genomic alterations.

9.2.4 Determine the repertoire of humoral responses

An array of serological assays will be used to evaluate the repertoire of antibody responses induced by treatment. Specifically antibodies from subject serum collected throughout treatment will be analyzed for reactivity to known tumor-associated antigens including but not limited to: cancer-testis (NY-ESO-1, MAGE-A3, SSX2, PRAME, etc.) and other tumor antigens (TP53, WT1, SOX2, etc.) using high-throughput semi-automated ELISA (BioTek) and may also use Seromics, a novel antibody profiling method utilizing protein microarrays with the capacity to detect circulating antibodies induced by the treatment against >8000 full-length human antigens

9.2.5 Determine the induction and the quality of the T cell responses

It is acknowledged that the tumors in this trial may not share tumor-associated antigens that can be studied across all subjects. Therefore, an effort will be made to identify tumor antigens for each subject using strategies including, but not limited to, collating the "antigenome" using seromics and immunohistochemistry data as well as identifying mutation-derived tumor antigens through genome sequencing and computational biology approaches to predict epitope: MHC binding affinity. Subject HLA typing will be done by sequence specific oligonucleotide probing and sequence specific priming of genomic DNA using standard procedures. T-cell responses will be detected using standard ELISPOT and intracellular cytokine assays.

9.2.6 Determine the correlation between the PD-L1 expression in primary tumor specimens and metastatic tumor specimens

The rationale for this analysis is that while PD-L1 expression by tumor cells has been correlated with response to drugs targeting PD-1/PD-L1 signaling, uncertainties remain regarding the optimal assay, optimal cut-point, and optimal source of tissue. For example, many prior analyses have correlated outcomes to PD-1 blockade with tumor expression of PD-L1 as assessed from primary archival tumor specimens. The correlation between PD-L1 expression in primary tumor specimens and metastatic specimens is unknown. Furthermore, the impact of first-line chemotherapy on PD-L1 expression is unknown. Therefore, in this exploratory analysis, PD-L1 expression in archival primary tumor specimens will be correlated with PD-L1 expression in metastatic post-chemotherapy tumor biopsies to generate data to refine our understanding of the optimal setting, assay, and cut-points, for use of PD-L1 as a predictive biomarker for future definitive randomized studies. Subjects agreeing to the sub study must have archival primary tumor specimens available for PD-L1 expression analysis in addition to undergoing a biopsy of a metastatic site.

9.3 Preparation and Shipment of Study Specimens

See Correlative Laboratory Manual for collection, processing and shipping instructions for all tissue and blood specimens.

9.4 Banking of Leftover Specimens

Subject consent will be obtained to bank any leftover samples collected for study-specific correlative research. Hoosier Cancer Research Network (HCRN) will manage the banked samples. Samples will be de-identified and banked indefinitely in the Hoosier Cancer Research Network Biorepository and used for future unspecified cancer-related research.

10 STUDY DRUG INFORMATION

10.1 Pembrolizumab

10.1.1 Chemical name and properties

Humanized X PD-1_mAb (H409A11) IgG4

10.1.2 Availability

Pembrolizumab is an investigational drug for this disease state and is not available outside of a clinical trial. Merck will supply the pembrolizumab.

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

10.1.3 Product Descriptions

Clinical Supplies will be provided by Merck as summarized below:

Product Name & Potency	Dosage Form
Pembrolizumab 100 mg/ 4mL	Solution for Injection

All other products will be supplied locally by the trial site.

10.1.4 Packaging and Labeling Information
Clinical supplies will be affixed with a clinical label in accordance with regulatory requirements.

10.1.5 Clinical Supplies Disclosures
The subject and site investigator are blinded to the protocol therapy assignment. For purposes of protocol therapy distribution, all administrators of the EDC system at HCRN and participating site pharmacy personnel will be unblinded to the protocol therapy assignment.

Clinical supplies must be stored in a secure, limited-access location under the storage conditions specified on the label. Clinical supplies may not be used for any purpose other than that stated in the protocol.

Receipt and dispensing of trial medication must be recorded by an authorized person at the trial site.

10.1.6 Adverse Events
Please refer to the current version of the Investigator's Brochure for a complete list of adverse events.

Pembrolizumab is generally well tolerated and demonstrates a favorable safety profile in comparison to chemotherapy. Pembrolizumab is an immunomodulatory agent, and based on this mechanism of action, immune mediated adverse events (IMAEs) are of primary concern. Important identified risks for pembrolizumab are of an immune mediate nature, including pneumonitis, colitis, hypophysitis (including hypothryoidism/hyperthyroidism), hepatitis, Type I diabetes mellitus, uveitis, and nephritis, myositis, Guillain-Barre syndrome, pancreatitis, and severe skin reaction toxic epidermal necrolysis (TEN), some with fatal outcome. A new important risk of myocarditis has been identified; cases with fatal outcome have been reported.

The majority of IMAEs was mild to moderate in severity, manageable with appropriate care, and rarely required discontinuation of therapy.

11 ADVERSE EVENTS
The descriptions and grading scales found in the NCI CTCAE v4 will be utilized for AE assessment. A copy of the CTCAE v4 can be downloaded from the CTEP website at http://ctep.cancer.gov. All forms for AE/SAE recording and reporting can be found in the Study Procedure Manual or in the EDC system (Documents and Information Tab).

11.1 Definition of Adverse Events

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

- Unintended or unfavorable sign or symptom
- A disease temporally associated with participation in the protocol

- An intercurrent illness or injury that impairs the well-being of the subject

Abnormal laboratory values or diagnostic test results constitute AEs only if they induce clinical signs or symptoms or require treatment or further diagnostic tests
Hospitalization for elective surgery or routine clinical procedures that are not the result of an AE (e.g., surgical insertion of central line) should not be recorded as an AE.

11.1.2 Serious Adverse Event

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

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

11.1.3 Suspected Adverse Reaction

Suspected adverse reaction means any AE for which there is a reasonable possibility that the study drug caused the adverse event. For the purposes of IND safety reporting, ‘reasonable possibility’ means there is evidence to suggest a causal relationship between the drug and the adverse event. A suspected adverse reaction implies a lesser degree of certainty about causality than adverse reaction, which means any adverse event caused by a drug.

11.1.4 Adverse Reaction

An adverse reaction means any AE caused by a drug. Adverse reactions are a subset of all suspected adverse reactions where there is reason to conclude that the drug caused the event.

11.1.5 Expected Adverse Event

Expected AEs are those events that have been previously identified as resulting from administration of the agent. For this study, an AE is considered expected when it appears in the current AE list, the Investigator’s Brochure (IB), the package insert or is included in the informed consent document as a potential risk.

11.1.6 Relatedness

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

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

11.2 Reporting

11.2.1 AE Reporting

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

11.2.2 SAE Reporting

11.2.2.1 Site Requirements for Reporting SAEs to HCRN

- SAEs will be reported from time of signed informed consent until 90 days after discontinuation of study drug(s).
- SAEs will be reported on the SAE/ECI Submission Form **within 24 hours** of discovery of the event.
- SAEs include events related and unrelated to the study drug(s).
- All SAEs will be recorded in the subject's medical record and on the appropriate study specific eCRF form within the EDC system.
- All SAEs regardless of relation to study drug will be followed until resolution to ≤ Grade 1 or baseline and/or deemed clinically insignificant and/or until a new anti-cancer treatment starts, whichever occurs first.

The SAE/ECI Submission Form may be submitted to HCRN electronically to safety@hoosiercancer.org. The site investigator is responsible for informing the IRB and/or other local regulatory bodies as per local requirements.

The original copy of the SAE/ECI Submission Form and the email correspondence must be kept within the study file at the study site.

Once the SAE has resolved (see resolution guidelines listed in 11.2.1), sites must submit a follow-up SAE/ECI Submission Form within a reasonable timeframe to HCRN electronically to safety@hoosiercancer.org.

11.2.2.2 HCRN Requirements for Reporting SAEs to Merck

Hoosier Cancer Research Network will report any possibly related and unexpected SAE to Merck **within one business day** of receipt of the SAE/ECI Submission Form and to regulatory authorities (FDA) per federal guidelines. Follow-up information will be provided to Merck as it is received from site.

11.3 Sponsor-Investigator Responsibilities

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

11.4 HCRN Responsibilities to FDA

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

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

11.5 IND Safety Reports Unrelated to this Trial

Merck will provide to HCRN IND safety reports from external studies that involve the study drug(s) per their guidelines. HCRN will forward safety reports to the sponsor-investigator who will review these reports and determine if revisions are needed to the protocol or consent. HCRN will forward these reports to participating sites within 1 business day of receiving the sponsor-investigator's review. Based on the sponsor-investigator's review, applicable changes will be made to the protocol and informed consent document (if required). All IND safety reports will also be made available to sites via the EDC system.
Upon receipt from HCRN, site investigators (or designees) are responsible for submitting these safety reports to their respective IRBs, as per their IRB policies.

11.6 Reporting of Pregnancy and Lactation to the Sponsor-Investigator and to Merck

Although pregnancy and lactation are not considered adverse events, it is the responsibility of site investigators or their designees to report any pregnancy or lactation in a subject (spontaneously reported to them), including the pregnancy of a male subject's female partner that occurs during the trial or within 120 days of completing the trial. All subjects and female partners of male subjects who become pregnant must be followed to the completion/termination of the pregnancy. Pregnancy outcomes of spontaneous abortion, missed abortion, benign hydatidiform mole, blighted ovum, fetal death, intrauterine death, miscarriage, and stillbirth must

be reported as serious adverse events. If the pregnancy continues to term, the outcome (health of infant) must also be reported.

Such events must be reported **within 24 hours** to HCRN. HCRN will report such events to the sponsor-investigator and Merck Global Safety **within one business day** of receiving notification of the event. (Attn: Worldwide Product Safety; FAX 215-993-1220)

11.7 Events of Clinical Interest

Events of Clinical Interest (ECI) described below must be recorded as such on the SAE/ECI Submission Form and reported **within 24 hours** to safety@hoosiercancer.org at HCRN. HCRN will report these events within **one business day** of receipt to Merck Global Safety. (Attn: Worldwide Product Safety; FAX 215 993-1220).

Events of clinical interest for this trial include:

1. an overdose of Funder's product that is not associated with clinical symptoms or abnormal laboratory results. For purposes of this trial, an overdose will be defined as any dose exceeding the prescribed dose for pembrolizumab greater than 10mg/kg over the prescribed dose. No specific information is available on the treatment of overdose of pembrolizumab. In the event of overdose, pembrolizumab should be discontinued and the subject should be observed closely for signs of toxicity. Appropriate supportive treatment should be provided if clinically indicated. If an adverse event(s) is associated with ("results from") the overdose of a Merck product, the adverse event(s) is reported as a serious adverse event, even if no other seriousness criteria are met.

2. an elevated AST or ALT lab value that is greater than or equal to 3X the upper limit of normal and an elevated total bilirubin lab value that is greater than or equal to 2X the upper limit of normal and, at the same time, an alkaline phosphatase lab value that is less than 2X the upper limit of normal, as determined by way of protocol-specified laboratory testing or unscheduled laboratory testing.*

   ***NOTE**: These criteria are based upon available regulatory guidance. The purpose of the criteria is to specify a threshold of abnormal hepatic tests that may require an additional evaluation for an underlying etiology.

12 STATISTICAL CONSIDERATION

12.1 Study design

This is a multi-institutional, randomized, placebo controlled, double-blinded phase II trial. Eligible subjects will be 1:1 randomized to placebo (Control Arm A) and pembrolizumab (Experimental Arm B). Stratification factors for randomization include: presence of visceral metastatic disease (lung, liver, or bone vs. none) at the time of initiation of first-line chemotherapy, and response to first-line chemotherapy (CR/PR vs. SD).

12.2 Definition of primary endpoint

The primary endpoint is progression–free survival (PFS), which is defined as the time from randomization to death or progression, depending on which occurs first, as per immune-related RECIST (irRECIST).

12.3 Definitions of secondary endpoints

- PFS, which is defined as the time from randomization to death or progression, depending on which occurs first as defined by RECIST 1.1.
- PFS as per irRECIST and RECIST 1.1 by PD-L1 expression levels.
- Six-month PFS rate, which is defined as the percentage of participants that are alive and progression-free, as per irRECIST and RECIST 1.1, at six months calculated from the date of randomization.
- Six-month PFS rate as per irRECIST and RECIST 1.1 by PD-L1 expression levels.
- Safety of pembrolizumab, defined as rates of Grade 1-5 toxicity according to CTCAE v4.0.
- Objective response rate (ORR) in subjects on maintenance pembrolizumab versus placebo, which is defined by irRECIST and RECIST 1.1 in subjects with measurable disease.
- ORR in subjects receiving pembrolizumab after progressing on placebo as per irRECIST and RECIST 1.1.
- Overall survival (OS), which is defined as the time from randomization to death.

12.4 Exploratory endpoints

- PFS and 6-month PFS as per irRECIST and RECIST 1.1 without visceral metastatic disease randomized to pembrolizumab versus placebo.
- Compare PD-L1 expression in primary tumor tissue and metastatic post first-line chemotherapy tumor tissue in a subgroup of subjects.
- Correlate immune infiltrates in tumor tissue with response rate, progression-free survival, and overall survival in subjects receiving pembrolizumab versus placebo
- Determine the repertoire of humoral responses and correlate with response rate, progression-free survival, and overall survival
- Determine the induction of T cell responses and correlate with response rate, progression-free survival, and overall survival
- Correlate genomic alterations with response rate, progression-free survival, and overall survival
- Correlate tobacco history with PFS in subjects receiving pembrolizumab versus placebo

12.5 Analysis plan for primary objective

We assume that treatment group will experience three phases in terms of treatment effect: no effect, partial effect, and full effect. Specifically, we assume that before month 2, there is no treatment effect and after month 3 there is full treatment effect. In terms of hazard ratio, it is 1 before month 2, and a target value θ <1 after month 3. The decrease of the hazard ratio from 1 to θ between month 2 and 3 does not need to be specified and can take any pattern.

We set the target value θ of the full treatment effect hazard ratio as 0.462. This target value is determined from the following rationale. The 12 months PFS survival is 6.2% for the control arm

and 16.8% for the treatment arm from the KEYNOTE-045 trial.[28] Assuming a constant hazard for the control group, we can obtain the hazard for the control arm is 0.232. From Figure 1B of Bellmunt et al 2017, we assume the treatment reaches its full effect around month 8. This corresponds to a full treatment effect hazard ratio of 0.462.

The sample size is determined by inverting the test statistic proposed by Zucker and Lakatos.[44] We set the type I error as 0.05 and power as 80%. Assuming the study duration is 3 years, the required total sample size based on one-sided test is at least 104 evaluable subjects (~52 per group). Therefore, the sample size is inflated to 108 to account for potential non-evaluable patients/early drop out. Censoring is assumed uniformly between month 6 and the end of study.

12.6 Analysis plan for secondary objectives

PFS will also be compared between Arms A and B using a weighted logrank test. The weight is 0 before month 2 and 1 after month 3. The form of the weight between month 2 and 3 will take a form specified in Equation (5) of Zucker and Lakatos.[44] This weighted log-rank test is used due to its maximum efficiency. The time points (months 2 and 3) are chosen based on our belief that that treatment is likely to have minimal effect before month 2 and reach its full effect after month 3. We will also compare the PFS using the usual constant weight logrank test. PFS will also be estimated by the Kaplan-Meier method and the estimated curves will be plotted. Median PFS for both groups will be estimated and their two-sided 95% confidence intervals will be constructed.

Comparison of the 6-month PFS between the two arms will be conducted using estimates from the Kaplan-Meier method and the Greenwood formula. The resulting test is a Chi-square type of test [43]. Subjects will be analyzed as they are randomized, regardless of the treatment that they actually receive. Data at the end of the 12-month follow-up period of the last treated patient will be used for analyses. For the placebo group, data before cross-over will be used for the analyses of primary objective. The evaluable set will be used for this analysis. PFS with respect to PD-L1 expression levels and OS will be estimated by Kaplan-Meier methods and the comparisons will be performed by logrank tests. Their medians will be estimated with 95% confidence intervals. HRs for both PFS and OS will be estimated using Cox proportional hazard models. Covariate effects will be evaluated by Cox proportional hazard models. RMST will be estimated based on the Kaplan-Meier estimates of the survival functions. ORR for pembrolizumab maintenance, placebo, and pembrolizumab after progression on placebo will be summarized by frequencies and percentages. Comparisons of rates will be performed by Pearson's chi-square tests or Fisher's exact tests. Durations of response will be summarized by median (1^{st}, 3^{rd} quartiles) and be compared using Wilcoxon rank sum test. These analyses will be performed using the evaluable set.

Adverse events for the safety of pembrolizumab will be summarized using frequencies and percentages with respect to grade levels. The safety set will be used for these analyses.

12.7 Exploratory analysis

Cohen's kappa and its 95% confidence interval will be calculated for PD-L1 expression between primary tumor tissue and metastatic post first-line chemotherapy tumor tissue in n=14 subjects. This sample size will lead to a power of 0.80 to detect a kappa≥0.70 against the null hypothesis kappa=0. Otherwise, the statistical analysis for correlative endpoints will be descriptive and

hypothesis generating in nature. Descriptive statistics, statistical plot, correlations and appropriate statistical modeling will be used.

12.8 Safety stopping rule

The Data and Safety Monitoring Board will examine the overall safety data regularly and decide whether the trial should continue as detailed in Section 13 based on the totality of the data. In addition, a stopping rule will be employed after 25 and 50 subjects finish at least one cycle of treatment in the Experimental Arm B, respectively. This safety stopping rule will be performed with respect to two criteria: definitely treatment-related deaths and grade 4 treatment-related AEs. Two-sided 90% exact binomial confidence intervals (CIs) will be constructed. If their lower bounds exceed pre-defined levels, the study drug will be considered unacceptably toxic for this patient population and the study will be terminated.

The package insert of another monoclonal antibody to PD1 indicates a fatal pneumonitis rate of 0.3-0.9%[44]. In addition, there have been other rare fatal events described with PD1 blockade. Consequently, if the lower bounds of the CIs of definitely treatment-related death rate exceed 0.9%, the study will be terminated. This corresponds to ≥ 2+ (2 or more) out of 25 and ≥ 3+ out of 50 subjects in the Experimental Arm B.

Previous studies reported a rate of 12% for grade 3-4 AEs.[27] Since the expected median PFSs are small for this patient population, we choose to focus on treatment-related grade 4 AEs. A rate of 10% is chosen that if the lower bounds of the CIs exceed 10%, enrollment will be halted and the study will be reviewed for continuation by the Data and Safety Monitoring Board. This corresponds to 6+ out of 25 and 10+ out of 50 subjects in the Experimental Arm B.

There will be no planned interim efficacy assessment.

12.9 Unblinding plan

For purposes of protocol therapy distribution, all administrators of the EDC system at HCRN and participating site pharmacy personnel will be unblinded to the protocol therapy assignment. For the purpose of the interim analyses and the final analysis, the statistician and HCRN analysis staff will be unblinded.

Unblinding of the protocol therapy will occur at the time of disease progression or discontinuation of protocol therapy due to unacceptable toxicity (see Section 6), which are considered as medical emergencies. Please see Section 7.3.2 for additional information on unblinding.

Subjects randomized to treatment with placebo will be eligible to cross over for treatment with pembrolizumab provided that eligibility outlined in Section 3 is still met.

12.10 Analysis datasets

- Enrolled set. This will comprise all subjects who meet the eligibility criteria and are registered onto the study.
- Evaluable set. This will comprise all enrolled subjects who undergo at least one post-baseline assessment or die before any evaluation.

- Safety set. This will comprise all subjects that receive at least one dose of study drug.

12.11 Sample size calculation/Accrual/Study duration/Replacement rules
As described in section 12.5.

12.12 Subject characteristics and significant protocol violations
Demographic and other baseline data will be summarized descriptively for all subjects in the enrolled set. Significant protocol violations will be documented.

12.13 Concomitant medication
Concomitant medications and significant non-drug therapies prior and after the start of the study drug will be summarized for the safety set.

12.14 Disposition
The number of enrolled subjects will be summarized in a flow chart with frequency of completion and discontinuation. The subjects discontinued from study drug and their corresponding information will be listed. Significant protocol violations will be tabulated and/or listed.

13 TRIAL MANAGEMENT

13.1 Data and Safety Monitoring Plan
This study will be conducted in accordance with Tisch Cancer Institute (TCI) at the Icahn School of Medicine at, Mount Sinai Medical Center (MSMC) Safety Monitoring Plan.

HCRN oversight activities include:
- Review all adverse events requiring expedited reporting as defined in the protocol
- Provide trial accrual progress, safety information and data summary reports to the sponsor-investigator
- Submit data summary reports to the DSMB for review according to DSMB Charter

13.2 Data Safety Monitoring Board
The Data Safety Monitoring Committee (DSMC) at Tisch Cancer Institute (TCI) at the Icahn School of Medicine at, Mount Sinai Medical Center (MSMC) will serve as the primary Data and Safety Monitoring Board (DSMB) for this trial. They will review and monitor study progress, toxicity, safety and other data from this trial. Questions about subject safety or protocol performance will be addressed with the sponsor-investigator, statistician and study team members. Should any major concerns arise; the DSMB will offer recommendations regarding whether or not to suspend the trial.

The DSMB will meet quarterly and information provided may include: subject accrual, treatment regimen information, adverse events and serious adverse events reported by category, summary of any deaths on study, audit and/or monitoring results.

The DSMB will provide a recommendation to the team after all information is reviewed. This information should also be provided to the IRB at the time of continuing review for the trial.

13.3 Data Quality Oversight Activities by HCRN

Remote validation of the EDC system data will be completed on a continual basis throughout the life cycle of the study. A summary report (QC Report) of these checks together with any queries resulting from manual review of the eCRFs will be generated for each site and transmitted to the site and the site monitor. Corrections will be made by the study site personnel.

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

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

13.4 Compliance with Trial Registration and Results Posting Requirements

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

14 DATA HANDLING AND RECORD KEEPING

14.1 Data Management

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

14.2 Case Report Forms and Submission

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

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

14.3 Record Retention

To enable evaluations and/or audits from Health Authorities/HCRN, the site investigator agrees to keep records, including the identity of all subjects (sufficient information to link records; e.g., hospital records), all original signed informed consent forms, copies of all source documents, and detailed records of drug disposition. All source documents are to remain in the subject's file and retained by the site investigator in compliance with the site contract with HCRN. No records will be destroyed until HCRN confirms destruction is permitted.

14.4 Confidentiality

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

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

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

15 ETHICS

15.1 Institutional Review Board (IRB) Approval

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

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

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

15.2 Ethical Conduct of the Study

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

15.3 Informed Consent Process

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

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

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APPENDIX

Appendix A Smoking History Questionnaire

1. Have you smoked at least 100 cigarettes in your entire life (do not include cigars or marijuana)?

YES.....1
NO.....2
DON'T KNOW.....9

2. How old were you when you first started to smoke cigarettes fairly regularly?

ENTER AGE IN YEARS |__|__|

NEVER SMOKED CIGARETTES REGULARLY.....2
DON'T KNOW.....9

3. Do you now smoke cigarettes?

EVERY DAY.....1
SOME DAYS.....2
NOT AT ALL.....3
DON'T KNOW.....9

4. How long has it been since you quit smoking?

ENTER NUMBER (OF DAYS, WEEKS, MONTHS, OR YEARS) |__|__|__|

ENTER UNIT
DAYS.....1
WEEKS.....2
MONTHS.....3
YEARS.....4

I AM STILL SMOKING.....5
DON'T KNOW.....9

5. At the time that you quit smoking, about how many cigarettes did you usually smoke per day?

1 pack equals 20 cigarettes
If less than 1 per day, enter 1
If 95 or more per day, enter 95

ENTER NUMBER OF CIGARETTES PER DAY |__|__|__|
I AM STILL SMOKING……..5
DON'T KNOW……9

6. During the past 30 days, on how many days did you smoke cigarettes?

ENTER NUMBER OF DAYS |__|__|
DON'T KNOW……9

7. During the past 30 days, on the days that you smoked, how many cigarettes did you smoke per day?

1 pack equals 20 cigarettes
If less than 1 per day, enter 1
If 95 or more per day, enter 95

ENTER NUMBER OF CIGARETTES PER DAY |__|__|__|
DON'T KNOW……9