University of California, Los Angeles

Phase Ib Trial of Pembrolizumab (MK-3475) with Platinum-based Chemotherapy in Small Cell/Neuroendocrine Cancers of Urothelium and Prostate

Principle Investigator: Arnold Chin, M.D.
Protocol: 22 May 2022

NCT Number: NCT03582475

SPONSOR:
University of California, Los Angeles
Institute of Urologic Oncology
Department of Urology
[redacted]

PRINCIPAL INVESTIGATOR:
Arnold I. Chin, MD, PhD
Associate Professor of Urology
University of California, Los Angeles

TITLE: Phase Ib Trial of Pembrolizumab (MK-3475) with Platinum-based Chemotherapy in Small Cell/Neuroendocrine Cancers of Urothelium and Prostate

IND NUMBER: [redacted]

UCLA Study Team
[redacted] Drakaki, MD, PhD
Assistant Professor of Hematology and Oncology

[redacted] Liu, MD
Assistant Professor of Hematology and Oncology

[redacted] Rettig, MD
Professor of Hematology and Oncology

[redacted] Shen, MD
Assistant Professor of Hematology and Oncology

[redacted]
Professor of Biostatistics

1.0 TRIAL SUMMARY

Abbreviated Title	Pembrolizumab (MK-3475) with Platinum-based Chemotherapy in Small Cell/Neuroendocrine Cancers of Urothelium and Prostate
Trial Phase	Phase Ib
Clinical Indication	The treatment of subjects with locally advanced or metastatic 1) naïve small cell cancer of the bladder (SCB), urethra, or upper urinary tract, and 2) primary small cell or neuroendocrine prostate cancer (NEPC)
Trial Type	Interventional
Type of control	No treatment control
Route of administration	Intravenous
Trial Blinding	Unblinded Open-label
Treatment Groups	Pembrolizumab 200 mg IV q3 weeks for up to 2 years Chemotherapy cycle q3 weeks for 4 to 6 cycles: Etoposide 100 mg/m^2 on day 1-3 + Cisplatin 70-80 mg/m^2 on day 1 OR Carboplatin 4-5 AUC on day 1 OR Docetaxel 60 mg/m^2 on day 1 + Carboplatin 4-5 AUC on day 1
Number of trial participants	Approximately 15 patients will be enrolled.
Estimated enrollment period	We estimate that the trial will require approximately 24 months from the time the first subject signs the informed consent until the last subject's consent.
Estimated duration of trial	We estimate that the trial will require approximately 36 months from the time the first subject signs the informed consent until the last subject's last study-related phone call or visit.
Duration of Participation	Each subject will participate in the trial from the time the subject signs the Informed Consent Form (ICF) through the final protocol-specified contact. After a screening phase of up to 28 days, eligible subjects will receive pembrolizumab on Day 1 of the 3-week (Q3W) dosing cycle and continue for a maximum of 35 cycles unless specific withdrawal/discontinuation criteria are met. Treatment with etoposide and cisplatin/carboplatin or docetaxel and carboplatin will occur on Day 1 for a maximum of 6 cycles unless specific withdrawal/discontinuation criteria are met. Treatment on trial will continue until verification of disease progression, unacceptable adverse event(s), intercurrent illness that prevents further administration of treatment,

	investigator's decision to withdraw the subject, subject withdraws consent, pregnancy of the subject, non-compliance with trial treatment or procedure requirements, or administrative reasons. Upon progression on treatment, patients will be asked to undergo an additional biopsy and blood draw. After the end of treatment, each subject will be followed for 30 days for adverse event (AE) monitoring. Serious AEs will be collected for 90 days after the trial treatment or 30 days after the end of treatment if the subject initiates new anti-cancer therapy, whichever is earlier. All drug-related SAEs will be reported regardless of time frame. All subjects will be followed for overall survival every 12 weeks until death, withdrawal of consent, or the end of the trial.
Estimated average length of treatment per patient	Average length of treatment per patient can range from 4 to 24 months.

2.0 TRIAL DESIGN

2.1 Trial Design

This is a non-randomized, multi-center, multi-cohort, open-label, Phase Ib trial of pembrolizumab (MK-3475) in combination with standard-of-care cisplatin-based chemotherapy in subjects with locally advanced or metastatic, 1) naïve small cell cancer of the bladder (SCB), urethra, or upper urinary tract, and 2) primary small cell or neuroendocrine prostate cancer (NEPC). Chemotherapy will include etoposide and cisplatin/carboplatin for Cohorts 1 and 2, with the option of docetaxel and carboplatin for Cohort 2.

Approximately 15 subjects will be enrolled in the trial with 7-8 subjects per cohort. Subjects will be enrolled regardless of programmed death-ligand 1 (PD-L1) status. Subjects must have measurable disease based on Response Evaluation Criteria in Solid Tumors (RECIST) 1.1 as determined by investigator/site radiologist.

For both cohorts, subjects must provide tumor tissue. For Cohort 1, an archival formalin-fixed paraffin-embedded (FFPE) tumor tissue within 6 months of screening is required. For Cohort 2, an archival formalin-fixed paraffin-embedded (FFPE) tumor from a soft tissue lesion or bone biopsy within 6 months of screening is required. Tumor blocks are preferred. Fresh frozen tissue will be an adjunct to FFPE. No new systemic anti-neoplastic therapy may be administered between the biopsy and initiating study medication. The qualifying biopsy does not need to be obtained after consent for this trial is signed.

In both cohorts, subjects will receive pembrolizumab 200 mg on day 1 for each 3-week cycle (Q3W). Chemotherapy will consist of etoposide 100 mg/m^2 on day 1-3 and cisplatin 70-80 mg/m^2 or carboplatin 4-5 AUC on day 1 for both Cohorts 1 and 2. Carboplatin will be substituted for cisplatin-ineligible subjects. Cohort 2 has an option for docetaxel 60 mg/m^2 on day 1 and

carboplatin 4-5 AUC on day 1. Subjects will receive 4-6 cycles of chemotherapy with a maximum 35 doses of pembrolizumab.

Subjects with small cell of the urothelium may undergo surgery of primary disease site and regional lymph nodes (e.g. radical cystectomy or nephroureterectomy) as standard-of-care therapy after chemotherapy. Pembrolizumab may be held to allow recovery and then to continue on study. Tissue and blood may be obtained at the time of surgery. Subjects with primary small cell of the prostate may undergo surgery or radiation of primary disease and regional lymph nodes as standard-of-care after chemotherapy. Pembrolizumab may be held to allow recovery and then to continue on study. Tissue and blood may be obtained at the time of surgery or prior to radiation.

The primary objective of this trial is to evaluate the preliminary efficacy of pembrolizumab (MK-3475) in combination with standard-of-care cisplatin-based chemotherapy by assessing the durable response rate (DRR), overall response rate (ORR), duration of response (DOR), and progression free survival (PFS) by RECIST 1.1 and overall survival (OS) in Cohorts 1 and 2, in addition to radiographic PFS (rPFS) by PCWG3 and PSA response in Cohort 2 [1]. The secondary objectives are to determine the safety and tolerability of pembrolizumab in combination with etoposide and cisplatin/carboplatin or docetaxel and carboplatin assessed by parameters of adverse events (AEs) The exploratory objectives are to correlate response to treatment with tissue and serum biomarkers including PD-L1 expression.

Central safety and efficacy will be monitored by the UCLA data safety and monitoring board (DSMB). Adverse events will be monitored throughout the trial and graded in severity according to the guidelines outlined in the NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0. Subjects showing clinical benefit in the trial will be allowed to continue treatment regardless of a decision to stop enrollment or suspend the study.

Subjects will be evaluated initially at 9 weeks (63 +/- 14 days) with radiographic cross sectional imaging to assess response to treatment while on chemotherapy and then every 12 weeks (84 +/- 14 days, based on the date of the previous scan) thereafter until progression or up to approximately 2 years from time of treatment initiation. Additionally, in Cohort 2, bone scans will be evaluated in conjunction with cross sectional imaging. Prostate-specific antigen (PSA) levels will be measured every 6 weeks (± 3 days). All imaging obtained on study will be assessed using RECIST 1.1 for determination of DRR, ORR, DOR, and PFS, and for rPFS by PCWG3 in Cohort 2. Treatment on trial will continue until verification of disease progression, unacceptable AE(s), intercurrent illness that prevents further administration of treatment, investigator's decision to withdraw the subject, subject withdraws consent, pregnancy of the subject, non-compliance with trial treatment or procedure requirements, administrative reasons, or the subject has received 35 trial treatments of pembrolizumab. If subjects with radiographic progression are clinically stable or improved, an exception may be considered to continue treatment upon consultation with Sponsor.

After the end of trial treatment, each subject will be followed for 30 days for AE monitoring. Serious AEs will be collected for 90 days after trial treatment or 30 days after the end of treatment if the subject initiates new anti-cancer therapy, whichever is earlier.

Subjects who stop the trial treatment after receiving 35 administrations of pembrolizumab for reasons other than disease progression or intolerability or who attain a complete response (CR), may be eligible for up to 17 administrations of re-treatment upon experiencing disease progression at the discretion of the investigator if no cancer treatment was administered since the last dose of pembrolizumab, the subject still meets the safety parameters listed in the inclusion/exclusion criteria, and the trial remains open.

Subjects who experience disease progression will be asked to undergo an additional biopsy and blood draw. Subjects will have post-treatment follow-up for disease status until death, withdrawing consent, or end of the trial. All subjects will be followed for overall survival every 12 weeks until death, withdrawal of consent, or the end of the trial, whichever comes first.

Specific procedures to be performed during the trial, as well as their prescribed times and associated visit windows, are outlined in the Trial Flow Chart - Section 6.0. Details of each procedure are provided in the Trial Procedures - Section 7.0.

2.2 Trial Diagram

The trial design is depicted in Figure 1.

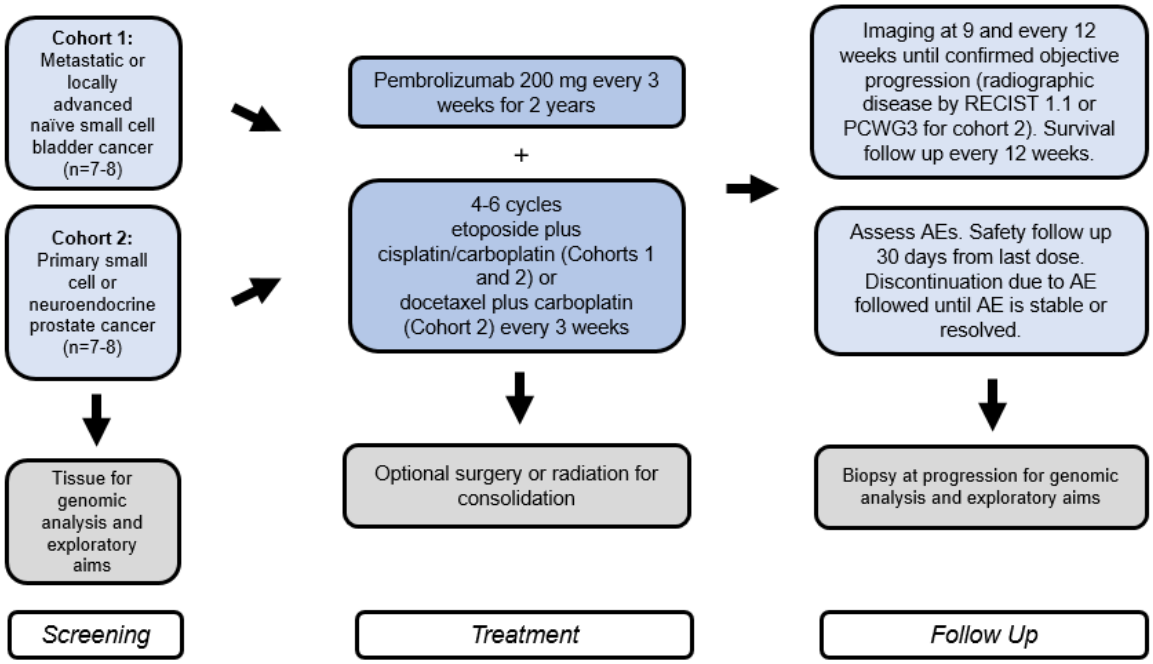


Figure 1 Trial Design

3.0 OBJECTIVE(S)

Safety and tolerability, will be assessed using all subjects. Additional objectives will be assessed by each cohort. There will be no hypothesis testing performed in this study.

3.1 Primary Objective

Objective: To evaluate the preliminary efficacy of pembrolizumab (MK-3475) in combination with standard-of-care cisplatin-based chemotherapy by assessing the durable response rate (DRR), overall response rate (ORR), duration of response (DOR), and progression free survival (PFS) by RECIST 1.1 and overall survival (OS) in Cohorts 1 and 2, and radiographic PFS (rPFS) by PCWG3 and PSA response in Cohort 2.

3.2 Secondary Objective

Objective: To determine the safety and tolerability of pembrolizumab in combination with etoposide and cisplatin/carboplatin or docetaxel and carboplatin assessed by parameters of adverse events (AEs).

3.3 Exploratory Objective

Objective: Determine correlation of biomarkers including PD-L1 expression (PD-L1 positive ≥1% by immunohistochemistry (IHC) using 22C3 antibody), and serum and tissue molecular (including genomic, proteomic) biomarkers that may be indicative of clinic response or safety.

4.0 BACKGROUND & RATIONALE

4.1 Background

Pembrolizumab is a potent humanized immunoglobulin G4 (IgG4) monoclonal antibody (mAb) with high specificity of binding to the programmed cell death 1 (PD-1) receptor, thus inhibiting its interaction with programmed cell death ligand 1 (PD-L1) and programmed cell death ligand 2 (PD-L2). Based on preclinical in vitro data, pembrolizumab has high affinity and potent receptor blocking activity for PD-1. Pembrolizumab has an acceptable preclinical safety profile and is in clinical development as an intravenous (IV) immunotherapy for advanced malignancies. Keytruda® (pembrolizumab) is indicated for the treatment of patients across a number of indications because of its mechanism of action to bind the PD-1 receptor on the T cell. For more details on specific indications refer to the Investigator Brochure (IB).

4.1.1 Pharmaceutical and Therapeutic Background

The importance of intact immune surveillance function in controlling outgrowth of neoplastic transformations has been known for decades [2]. Accumulating evidence shows a correlation between tumor-infiltrating lymphocytes in cancer tissue and favorable prognosis in various malignancies. In particular, the presence of $CD8^+$ T-cells and the ratio of $CD8^+$ effector T-cells/$FoxP3^+$ regulatory T-cells (T-regs) correlates with improved prognosis and long-term survival in solid malignancies, such as ovarian, colorectal, and pancreatic cancer; hepatocellular carcinoma; malignant melanoma; and renal cell carcinoma. Tumor-infiltrating lymphocytes can be expanded ex vivo and reinfused, inducing durable objective tumor responses in cancers such as melanoma [3,4].

The PD-1 receptor-ligand interaction is a major pathway hijacked by tumors to suppress immune control. The normal function of PD-1, expressed on the cell surface of activated T-cells under healthy conditions, is to down-modulate unwanted or excessive immune responses, including autoimmune reactions. PD-1 (encoded by the gene *Pdcd1*) is an immunoglobulin (Ig) superfamily member related to cluster of differentiation 28 (CD28) and cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) that has been shown to negatively regulate antigen receptor signaling upon engagement of its ligands (PD-L1 and/or PD-L2) [5,6].

The structure of murine PD-1 has been resolved [7]. PD-1 and its family members are type I transmembrane glycoproteins containing an Ig-variable–type (IgV-type) domain responsible for ligand binding and a cytoplasmic tail responsible for the binding of signaling molecules. The cytoplasmic tail of PD-1 contains 2 tyrosine-based signaling motifs, an immunoreceptor tyrosine-based inhibition motif, and an immunoreceptor tyrosine-based switch motif. Following T-cell stimulation, PD-1 recruits the tyrosine phosphatases, SHP-1 and SHP-2, to the immunoreceptor tyrosine-based switch motif within its cytoplasmic tail, leading to the dephosphorylation of effector molecules such as CD3 zeta (CD3ζ), protein kinase C-theta (PKCθ), and zeta-chain-associated protein kinase (ZAP70), which are involved in the CD3 T-cell signaling cascade [6,8–10]. The mechanism by which PD-1 down-modulates T-cell responses is similar to, but distinct from, that of CTLA-4, because both molecules regulate an overlapping set of signaling proteins [11,12]. As a consequence, the PD-1/PD-L1 pathway is an attractive target for therapeutic intervention.

4.1.2 Preclinical and Clinical Trial Data

Refer to the Investigator's Brochure (IB) for Preclinical and Clinical data.

4.1.3 Ongoing Clinical Trials

The use of pembrolizumab in small cell carcinomas is being studies in multiple clinical trials.

[redacted]

[redacted]

[redacted]

4.1.4 Information on Other Trial-Related Therapy

There is rationale to combine pembrolizumab with systemic chemotherapy. The use of pembrolizumab in combination with chemotherapy, namely pemetrexed and carboplatin, was FDA approved in May 2017 for non-small cell lung cancer ([redacted]) have been investigating the addition of pembrolizumab to chemotherapy in lung cancer, head and neck cancer, and gastric cancer, respectively, since February 2014. KEYNOTE-021 studies the use of pembrolizumab in combination with chemotherapies including paclitaxel and carboplatin. KEYNOTE-048 and KEYNOTE-059 studies pembrolizumab with or without cisplatin/carboplatin and 5-flourouracil (5-FU), and pembrolizumab with or without cisplatin and 5-FU, respectively.

[redacted]) is an ongoing phase III study with one arm investigating pembrolizumab in combination with gemcitabine and cisplatin/carboplatin in metastatic urothelial carcinoma, while [redacted] is an ongoing phase Ib/II study of pembolizumab and combination therapies including docetaxel for metastatic castrate-resistant prostate cancer (mCRPC), providing further support for combining pembrolizumab with cytotoxic chemotherapy. [redacted]) is an ongoing phase III study of pembrolizumab in combination with etoposide and cisplatin/carboplatin in SCLC as described in 4.1.3.

The combination of pembrolizumab and chemotherapy appears to be tolerated well. In KEYNOTE-021, grade 3 or higher toxicities were 39% versus 26% with treatment related deaths 2% versus 3% between the pembrolizumab and chemotherapy group versus chemotherapy monotherapy group. In the pembrolizumab and chemotherapy group the major toxicities were anemia 12%, neutropenia 5%, acute kidney injury, fatigue, leukopenia, thrombocytopenia, and sepsis (each 3%), while in the chemotherapy alone group there were anemia 15%, neutropenia, pancytopenia, thrombocytopenia (each 3%) [14].

[redacted]

4.1.4.1 Etoposide

Etoposide is a topoisomerase II inhibitor that complexes with DNA and prevents re-ligation of DNA strands leading to DNA strand breaks, errors in DNA synthesis, and promotes cellular apoptosis. It is approved for patients with SCLC and testicular cancer. Major adverse effects (>10%) include alopecia, nausea and vomiting, bone marrow suppression, and (1-10%) hypotension, peripheral neuropathy, stomatitis, hepatotoxicity, and hypersensitivity. The secondary occurrences of acute leukemia (<1%) have been reported after long term use.

Etoposide can be given for patients on dialysis. For patients on hemodialysis, dose will be reduced by 50% with administration on a non-dialysis day and then hemodialysis the following day. For patients on peritoneal dialysis, dose will be reduced by 50%, with dialysis performed daily [16].

Refer to package insert for complete drug information.

4.1.4.2 Docetaxel

Docetaxel promotes the assembly of microtubules in the cell and inhibits depolymerization of tubulin, which results in inhibition of DNA, RNA, and protein synthesis predominantly in the M phase of the cell cycle. It is indicated for patients with locally advanced or metastatic breast cancer, NSCLC, mCRPC, gastric adenocarcinoma, and squamous cell carcinoma of the head and neck cancer. Major adverse effects (>10%) include neuropathy, alopecia, fluid retention, stomatitis, bone marrow suppression, elevated transaminases, hypersensitivity, infection, weakness and myalgia, pulmonary toxicity, fever and (1-10%) decreased ejection fraction, motor neuropathy, dysgeusia, increased bilirubin, and arthralgia.

To reduce the severity of hypersensitivity reactions and fluid retention following administration, patients are typically premedicated with steroids and continue on steroids during the treatment cycle. In TAX 327, dexamethasone 8 mg was given 12, 3, and 1 hour prior to docetaxel infusion with prednisone 5 mg PO bid [17].

Refer to package insert for complete drug information.

4.1.4.3 Cisplatin

Cisplatin is a platinum-containing agent that inhibits DNA synthesis by formation of DNA crosslinks and is approved for patients with bladder, ovarian, and testicular cancer in combinational therapies. Off-label it is commonly used in combination for small cell carcinomas (NCCN guidelines) [18,19]. Major adverse effects (>10%) include neurotoxicity, nephrotoxicity, nausea and vomiting, bone marrow suppression, increase in liver enzymes, ototoxicity, and (1-10%) local irritation.

Cisplatin ineligibility is common [20]. Established guidelines (ie, NCCN and European Society of Medical Oncology [ESMO]) include the following considerations in determining if a subject is clinically ineligible for cisplatin: CTCAE v.4, Grade ≥2 peripheral neuropathy; CTCAE v.4, Grade

≥2 audiometric hearing loss (25 decibels in 2 consecutive wave ranges); CrCl <60 mL/min but ≥30 mL/min; New York Heart Association Class III heart failure; and ECOG PS of 2.

Dose of cisplatin is 70-80 mg/m^2 based on treating physician preference. Alternatively, for subjects with CrCl ≥30 and <60, cisplatin dose can be split 50% over two days with the first dose given Day 1 and second dose given Day 8 (± 3 Days).

Refer to package insert for complete drug information.

4.1.4.4 Carboplatin

Carboplatin is a second-generation platinum agent that is indicated for patients with ovarian cancer, and often used as a substitute in cisplatin-ineligible patients

Dose of carboplatin is AUC 4-5 based on treating physician preference. Glomerular filtration rate (GFR) can be determined using a variety of validated calculators, including but not limited to Cockroft-Gault, Jelliffe, or Modification of Diet in Renal Disease (MDRD) etc. Carboplatin can be used for patients on dialysis. For patients on hemodialysis, dose (in mg) will be target AUC x 25 to be administered on a non-dialysis day and then hemodialysis the following day. For patients on peritoneal dialysis, dose will be reduced by 75%, with dialysis performed daily [16].

Major adverse effects (>10%) include central nervous system pain, electrolyte abnormalities including hyponatremia and hypokalemia, nausea and vomiting, bone marrow suppression, increase in liver function tests, hypersensitivity, neuromuscular weakness, nephrotoxicity, and (1-10%) peripheral neuropathy, alopecia, constipation or diarrhea, bleeding complications, infection, increased bilirubin, visual disturbances, and ototoxicity.

Refer to package insert for complete drug information.

4.1.4.5 Response to Etoposide and Platinum (Cisplatin/Carboplatin) or Docetaxel and Carboplatin in Small Cell Cancers

The combination of etoposide and cisplatin is the mainstay chemotherapy regimen for SCLC based on clinical activity and toxicity profiles [21,22]. In SCLC, although response rates of 50-80% are seen in first-line treatment with etoposide and cisplatin, progression invariable occurs with poor outcomes to second-line therapies and median OS of 8 to 12 months and 2 year OS of 5% [13]. Thus, despite an initial high response rate, the etoposide and cisplatin doublet shows poor durability of responses.

Systemic therapy plays a major role in the treatment of small cell bladder and prostate carcinomas. In SCB there are no randomized clinical trials to base therapy, and regimens have been selected on retrospective data and small phase II trials. For localized SCB (including small cell urethral and upper urinary tract), systemic therapy using neoadjuvant etoposide and cisplatin followed by definitive local therapy improves clinical outcomes [23–25]. For metastatic SCB, etoposide and cisplatin is the preferred primary therapy with alternative agents including topotecan, anthracyclines, and vinca alkaloids [26,27].

As the majority of SCB have mixed histology, rationale strategies need to account for the urothelial carcinoma component. Cisplatin-based chemotherapy is the standard first-line treatment for patients with advanced urothelial carcinoma [28–30]. Carboplatin is often substituted for cisplatin, but is associated with inferior outcomes [31]. Thus, the combination of etoposide and cisplatin is the preferred regimen for SCB, with carboplatin reserved for cisplatin-ineligible patients.

A phase II trial in SCB showed a high, but transient response rate to either etoposide/cisplatin or ifosfamide/doxorubicin doublets, with a median overall survival of 13 months in the metastatic setting [32]. This further supports the poor DOR of small cell carcinomas to chemotherapy.

Primary small cell carcinoma of the prostate is a rare disease and is typically treated with etoposide and cisplatin chemotherapy, similar to the treatment of SCLC (NCCN guidelines) [33]. NEPC, in contrast, is a treatment-emergent disease of patients with metastatic castrate resistant prostate cancer (mCRPC) treated with androgen deprivation therapy (ADT), with phenotypes ranging from focal neuroendocrine with predominant adenocarcinoma, an intermediate histology between adenocarcinoma and small cell carcinoma, to pure small cell differentiated carcinoma [33]. Although few prospective trials have been conducted, current treatment includes cytotoxic chemotherapy with platinum-based regimens including etoposide and cisplatin with continued ADT [34].

Similar to SCLC and SCB, NEPC has a high response rate to etoposide and platinum-based chemotherapy, but at disease progression often exhibits adenocarcinoma. This suggests the need to address both histologic phenotypes of this disease and led to use of docetaxel, which is the standard first-line chemotherapeutic in mCRPC, in combination with platinum-based chemotherapy. A phase II study incorporated first-line docetaxel and carboplatin and second-line etoposide and cisplatin in 120 patients with “anaplastic” prostate cancer [35]. Because of toxicity concerns with cisplatin, carboplatin was used. While 65% were progression free after 4 cycles of docetaxel and carboplatin versus 33% with etoposide and cisplatin, median overall survival was 16 months.

These studies provide the evidence for use of etoposide and platinum-based chemotherapy for small cell cancers of the bladder and prostate, with the option of docetaxel and carboplatin for NEPC.

4.2 Rationale

4.2.1 Rationale for the Trial and Selected Population

Small cell carcinomas (SCC) are aggressive malignancies found in multiple tissue types including the lung, bladder, prostate, ovaries, and breast [36]. They belong to a larger family of histologically defined neuroendocrine cancers that include well-differentiated carcinoid, adenocarcinoma with neuroendocrine differentiation, and large-cell carcinomas. SCCs share common histologic and clinicopathologic features such as small, round-to-oval cells with high nuclear-to-cytoplasm ratios, frequent expression of markers such as neuron-specific enolase, synaptophysin, and chromogranin, rapid progression to metastatic dissemination, and relapse after response to chemotherapy [37]. These similarities infer a common molecular underpinning to the disease. Depending on the tissue of origin, and despite treatment with etoposide and platinum-based

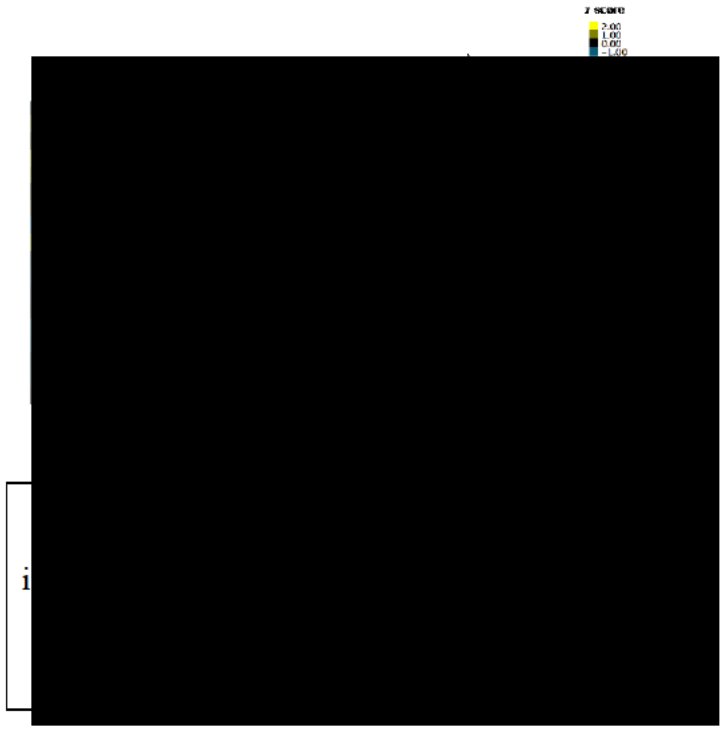
chemotherapy, 5-year survival rates are typically less than 20%, making the treatment of small cell carcinomas an unmet need [38]. This trial is aimed to generate data that can change the standard-of-care treatment of small cell carcinomas.

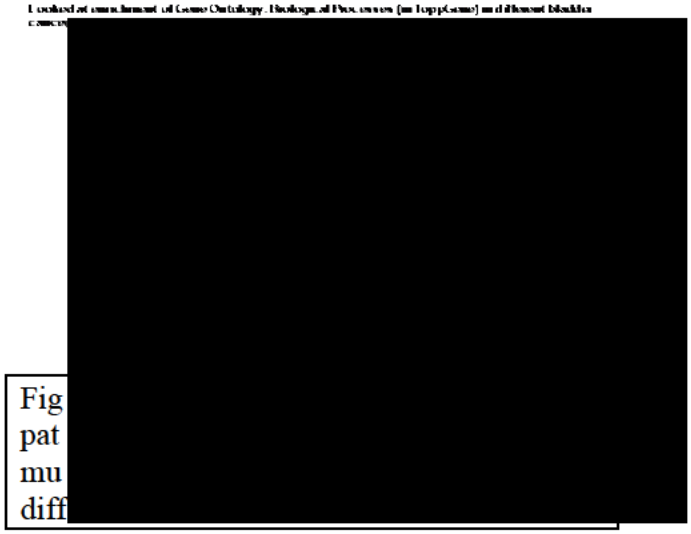
Bladder cancer incidence is over 430,000 cases worldwide and accounting for over 165,000 deaths, making it the ninth most common cancer [39]. Approximately 90% of bladder cancers are urothelial carcinomas, which arise from the urothelial epithelium and occur not only in the bladder, but also renal pelvis, ureter (upper urinary tract) and urethra. Small cell cancers of the bladder represent about 1% of bladder malignancies, and most commonly characterized as a mixed phenotype with urothelial carcinomas [40]. Small cell carcinomas are typically diagnosed by histology with poor utility of serum markers, and incomplete penetrance of histologic markers including neuron-specific enolase (25-100%), chromogranin A (22-89%), and synaptophysin (60-76%), as well as CK7, CD57, and CD56 [41]. Prognosis is worse than urothelial carcinoma with a 5-year overall survival rate of 19 to 25%. With high risk for metastatic disease, the clinical management for even localized tumors is primary chemotherapy with etoposide plus platinum chemotherapy followed by consolidative surgery if feasible (see Section 4.1.4.5). Carboplatin can be substituted in patients with cisplatin-ineligibility, including but not limited to impaired renal function, low performance status, or neurotoxicity.

Analysis of the updated bladder The Cancer Genome Atlas (TCGA) of 412 samples as well as a retrospective tissue cohort of 307 transurethral resected untreated muscle-invasive urothelial carcinoma have described a neuronal/neuroendocrine subtype associated with a poor prognosis that lacks expression of the typical histologic markers [42,43]. This implies that bladder cancers with a neuronal/small cell phenotype may be more pervasive than previously described.

Prostate cancer incidence is over 1,600,000 cases worldwide and one of the more common malignancies in men [44]. Small cell carcinomas of the prostate can arise *de novo,* which accounts for only approximately 1% of prostate cancer cases. However, a neuroendocrine prostate cancer (NEPC) that emerges in patients with mCRPC following treatment with ADT may occur in up to 20-40% of patients with mCRPC. NEPC includes up to 15% of pure small cell differentiated cancers and 25% with an intermediate phenotype [45]. Clinically, patients with NEPC may exhibit visceral metastases, lytic bone metastases, and disease burden out of proportion to the serum marker PSA [35]. As with small cell carcinomas of urothelial origin, detection can be challenging as serum or tissue neuroendocrine markers such as chromogranin A, synaptophysin, and neuron-specific enolase have limited sensitivity. CEA may be an emerging prognostic marker for NEPC [33,35]. Histology remains the standard for diagnosis of NEPC. Prognosis is poor, with a median overall survival ranging from 10 to 19 months [45]. With over 26,000 deaths from CRPC in the US and 360,000 worldwide, the potential 20-40% of patients with NEPC will be an increasingly significant unmet clinical need [44,46].

Studies from the UCLA Small Cell Collaborative Group have hypothesized that small cell cancers of different origins share molecular pathways and that insight into these mechanisms will lead to treatments universal to all small cell cancers. Research in small cell cancers of the bladder has been challenged by the lack of cell lines or animal models, with limited models in prostate cancer [47]. To date, archival FFPE tissue obtained at UCLA between 2008 to 2017 in 9 small cell bladder cancers and 9 muscle-invasive urothelial bladder cancers controls have been subjected to RNA sequencing analysis (RNA Seq) revealing distinct neuronal and stem cell-like genes preferentially expressed in the small cell versus muscle-invasive urothelial carcinomas (unpublished data) (Figure 2). This is supported by pathway enrichment using gene ontology groups (unpublished data) (Figure 3). Using rank-rank hypergeometric overlap (RRHO), we found that NEPC had a strong overlap with the molecular profile of SCLC, which further associated with SCB cancers (Figure 4). Analysis of additional samples is ongoing.





Small cell carcinomas have variable expression of PD-L1. Retrospective studies in 102 SCLC specimens showed expression of PD-L1 in tumor cells of 71% which correlated with overall survival [48]. A recent study in SCLC showed a small number of cases (2%) with amplification of PD-L1 [49]. In our initial cohort of SCB, 100% of specimens showed expression of PD-L1 defined by >1% expression in either cancer epithelium or stroma by immunohistoche mistry (SP142, SpringBio) (unpublished data). Preliminary studies in NEPC have supported increased expression of PD-L1 by gene expression.

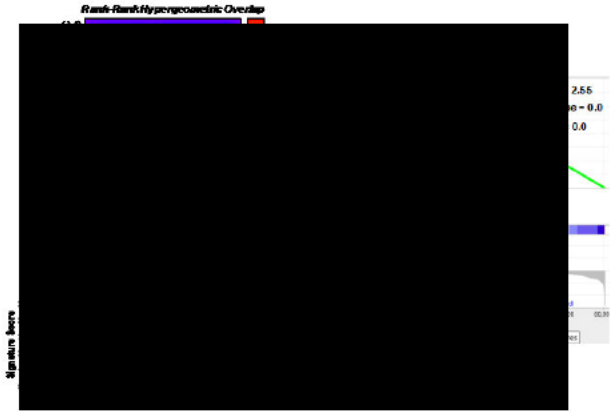


Figure 4. RNASeq expression data was assembled from studies of CRPC/NEPC and NSCLC/SCLC [56–58]. A differential expression test on the adenocarcinoma/small cell carcinoma for each tissue type was performed using DESeq2. Two ranked lists of genes were generated from the log *p*-values. Comparison of these two lists was performed using a rank-rank hypergeometric overlap algorithm, which gives a measure of the similarity of global expression profiles [59]. A small cell signature was generated by taking the top 50 genes by average rank across the lists. Signature scores are shown in the boxplots using a Z-score normalized sum of expression values on two independent datasets of prostate and lung cancer that contained small cell/neuroendocrine samples. For application to the bladder the 50 gene signature was inputted into a GSEA and ran on the small cell /MIBC dichotomy in the UCLA SCB cohort.

With the encouraging ORR of pembrolizumab in the heavily treated KEYNOTE-028 SCLC cohort, in conjunction with the biologic similarities among small cell carcinomas of the bladder, lung, and prostate, it is hypothesized that pembrolizumab will have a favorable response rate as first-line therapy in combination with chemotherapy in small cell carcinomas of the bladder and prostate. Aside for isolated case reports, currently no studies of checkpoint inhibitors have focused on the small cell histology of bladder or prostate cancer [50].

The present trial will be a non-randomized, multi-center, two-cohort, open-label, Phase Ib trial in subjects with small cell carcinoma of 1) naïve small cell cancer of the bladder, urethra, or upper urinary tract, and 2) primary small cell or neuroendocrine prostate cancer. The rationale for this trial is to elaborate the findings from prior and ongoing pembrolizumab trials in SCLC to small cell carcinomas of other epithelial types, namely bladder and prostate, as well as examine the synergistic effects of combining pembrolizumab with standard-of-care chemotherapy. The primary objective will be to estimate efficacy by a number of endpoints including durable response rate, overall response rate, duration of response, progression free survival, and overall survival, with secondary endpoints to assess safety and tolerability, as well as extend our understanding of this disease and response to therapy with exploratory analyses.

4.2.2 Justification for Dose

4.2.2.1 Pembrolizumab

The planned dose of pembrolizumab for this study is 200 mg every 3 weeks (Q3W). Based on the totality of data generated in the Keytruda development program, 200 mg Q3W is the appropriate dose of pembrolizumab for adults across all indications and regardless of tumor type. As outlined below, this dose is justified by:

- Clinical data from 8 randomized studies demonstrating flat dose- and exposure-efficacy relationships from 2 mg/kg Q3W to 10 mg/kg every 2 weeks (Q2W),
- Clinical data showing meaningful improvement in benefit-risk including overall survival at 200 mg Q3W across multiple indications, and
- Pharmacology data showing full target saturation in both systemic circulation (inferred from pharmacokinetic [PK] data) and tumor (inferred from physiologically-based PK [PBPK] analysis) at 200 mg Q3W

Among the 8 randomized dose-comparison studies, a total of 2262 participants were enrolled with melanoma and non-small cell lung cancer (NSCLC), covering different disease settings (treatment naïve, previously treated, PD-L1 enriched, and all-comers) and different treatment settings (monotherapy and in combination with chemotherapy). Five studies compared 2 mg/kg Q3W versus 10 mg/kg Q2W (KN001 Cohort B2, KN001 Cohort D, KN002, KN010, and KN021), and 3 studies compared 10 mg/kg Q3W versus 10 mg/kg Q2W (KN001 Cohort B3, KN001 Cohort F2 and KN006). All of these studies demonstrated flat dose- and exposure-response relationships across the doses studied representing an approximate 5- to 7.5-fold differences in exposure. The 2 mg/kg (or 200 mg fixed-dose) Q3W provided similar responses to the highest doses studied. Subsequently, flat dose-exposure-response relationships were also observed in other tumor types including head and neck cancer, bladder cancer, gastric cancer and classical Hodgkin Lymphoma, confirming 200 mg Q3W as the appropriate dose independent of the tumor type. These findings are consistent with the mechanism of action of pembrolizumab, which acts by interaction with immune cells, and not via direct binding to cancer cells.

Additionally, pharmacology data clearly show target saturation at 200 mg Q3W. First, PK data in KN001 evaluating target-mediated drug disposition (TMDD) conclusively demonstrated saturation of PD-1 in systemic circulation at doses much lower than 200 mg Q3W. Second, a PBPK analysis was conducted to predict tumor PD-1 saturation over a wide range of tumor penetration and PD-1 expression. This evaluation concluded that pembrolizumab at 200 mg Q3W achieves full PD-1 saturation in both blood and tumor.

Finally, population PK analysis of pembrolizumab, which characterized the influence of body weight and other participant covariates on exposure, has shown that the fixed-dosing provides similar control of PK variability as weight based dosing, with considerable overlap in the distribution of exposures from the 200 mg Q3W fixed dose and 2 mg/kg Q3W dose. Supported by these PK characteristics, and given that fixed-dose has advantages of reduced dosing complexity and reduced potential of dosing errors, the 200 mg Q3W fixed-dose was selected for evaluation across all pembrolizumab protocols.

Patient with end-stage renal disease on hemodialysis or peritoneal dialysis have more limited treatment options. However, pembrolizumab has been tolerated in hemodialysis and peritoneal dialysis patients without dose modifications [51–54]. In these patients, pembrolizumab will be given in combination with reduced dose etoposide and carboplatin. For patients on hemodialysis, pembrolizumab will be administered on non-dialysis days to coordinate with chemotherapy administration. There will be no administration changes for patients on peritoneal dialysis.

4.2.2.2 Chemotherapy

A number of trials have examined the combination of pembrolizumab with chemotherapy, including ongoing studies using pembrolizumab with etoposide, docetaxel, and cisplatin/carboplatin. Toxicities have not been available to review for combination studies in small cell cancers, but other studies have suggested side effects are similar to what is expected when the drugs are given separately and discussed in 4.1.4. The doses and schedules of chemotherapy have been based on these trials and will be the following: etoposide 100 mg/m^2 on day 1-3 and cisplatin 70-80 mg/m^2 on day 1 or carboplatin 4-5 AUC on day 1 with Q3W dosing; or docetaxel 60 mg/m^2 and carboplatin 4-5 AUC on day 1 with Q3W dosing. Dose modifications of etoposide and carboplatin for patients on dialysis are elaborated in 4.1.4.1 and 4.1.4.4.

4.2.3 Rationale for Endpoints

4.2.3.1 Efficacy Endpoints

For this phase Ib trial, the primary efficacy endpoints will be to estimate DRR, ORR, DOR, and PFS by RECIST 1.1 and OS for Cohorts 1 and 2, and for rPFS by PCWG3 in Cohort 2. In addition, in the prostate cancer cohort, PSA will be measured, but may not be reliable in this setting as NEPC often exhibits disease disproportionate to PSA [35]. Durable responses have been demonstrated with pembrolizumab in subjects with SCLC and DOR will also provide meaningful initial evidence for clinical efficacy.

4.2.3.2 Safety Endpoints

The primary safety objective of this trial is to characterize the safety and tolerability of pembrolizumab in combination with etoposide and cisplatin/carboplatin or docetaxel and carboplatin in subjects with small cell cancers of the bladder and prostate. The primary safety analysis will be based on subjects who experienced toxicities as defined by CTCAE Version 4.0 criteria. Safety will be assessed by quantifying the toxicities and grades experienced by subjects who have received pembrolizumab. The attribution to drug, time-of-onset, duration of the event, its resolution, and any concomitant medications administered will be recorded. Adverse events will be analyzed including but not limited to all AEs, SAEs, fatal AEs, and clinically significant laboratory changes. The mandatory Safety Follow-up Visit will be conducted approximately 30 days after the last dose of trial treatment or before the initiation of a new anti-neoplastic treatment, whichever comes first. All AEs that occur prior to the Safety Follow-up Visit should be recorded. Subjects with an AE of Grade >1 will be followed until the resolution of the AE to Grade 0-1 or until the beginning of a new anti- neoplastic therapy, whichever occurs first. Serious AEs will be collected for 90 days after the trial treatment or 30 days after the end of treatment if the subject initiates new anti-cancer therapy, whichever is earlier.

4.2.3.3 Biomarker Research

<u>Introduction</u>

Cancer immunotherapies represent an important and novel class of antitumor agents. However,

the mechanism of action of these exciting new therapies is not completely understood and much remains to be learned regarding how best to leverage these new drugs in treating patients. Thus, to aid future patients, it is important to investigate the determinants of response or resistance to cancer immunotherapy as well as determinants of AEs in the course of our clinical trials. These efforts will identify novel predictive biomarkers and generate information that will better guide single-agent and combination therapy with immuno-oncology drugs. To identify novel biomarkers, we will collect biospecimens (e.g., blood components, tumor material) to support analyses of cellular components (e.g., protein, DNA, ribonucleic acid [RNA], metabolites) and other circulating molecules. Investigations may include but are not limited to:

Germline (blood) Genetic Analyses (eg., single-nucleotide polymorphism analyses, whole exome sequencing, whole genome sequencing): This research will evaluate whether genetic variation within a clinical trial population correlates with response to the treatment(s) under evaluation. If genetic variation is found to predict efficacy or AEs, the data might inform optimal use of therapies in the patient population. Furthermore, it is important to evaluate germline DNA variation across the genome in order to interpret tumor-specific DNA mutations. Finally, microsatellite instability may be evaluated as this is an important biomarker for some cancers (ie, colorectal cancer).

Genetic (DNA) analyses from tumor: The application of new technologies, such as next-generation sequencing, has provided scientists the opportunity to identify tumor-specific DNA changes (e.g., mutations, methylation status, microsatellite instability). Key molecular changes of interest to immune-oncology drug development include the mutational burden of tumors and the clonality of T-cells in the tumor microenvironment. Increased mutational burden (sometimes referred to as a 'hyper-mutated' state) may generate neo-antigen presentation in the tumor microenvironment. Mutational load can be estimated by exome sequencing or targeted sequencing. To conduct this type of research, it is important to identify tumor-specific mutations that occur across all genes in the tumor genome. Thus, genome-wide approaches may be used for this effort. Note that in order to understand tumor-specific mutations, it is necessary to compare the tumor genome with the germline genome. Microsatellite instability may also be evaluated as this is an important biomarker for some cancers (ie, colorectal cancer). Microsatellite instability can be determined by PCR using a standard National Cancer Institute consensus of five microsatellite loci, including three dinucleotide repeat markers (D2S123, D5S346, D17S250) and two mononucleotide repeat markers (BAT 25 and BAT 26). Defects in mismatch repair genes can be determined by immunohistochemistry.

Tumor and blood RNA analyses: Both genome-wide and targeted mRNA expression profiling and sequencing in tumor tissue and in blood may be performed to define gene signatures that correlate to clinical response to treatment with pembrolizumab or other immunotherapies. Pembrolizumab induces a response in tumors that likely reflects an inflamed/immune phenotype. Specific immune-related gene sets (such as those capturing interferon-gamma transcriptional pathways) may be evaluated and new signatures may be identified. Individual genes related to the immune system may also be evaluated (e.g., IL- 10). MicroRNA profiling may also be pursued.

Proteomics and Immunohistochemistry (IHC) using Blood or Tumor: Tumor and blood samples from this study may undergo proteomic analyses (e.g., PD-L1 IHC). PD-L1 protein level in tumor sections, assessed by IHC, has been shown to correlate with response to pembrolizumab in subjects

with NSCLC, and an in vitro diagnostic (IVD) device has been developed for use with pembrolizumab in NSCLC. Preliminary data indicates that this association may also be true in additional cancer types (ie, triple-negative breast cancer, head and neck, and gastric). Additional tumor- or blood-derived proteins may also correlate with response to pembrolizumab. Therefore, tumor tissue may be subjected to proteomic analyses using a variety of platforms that could include, but are not limited to, flow cytometry, immunoassays, liquid chromatography/mass spectrometry. This approach could identify novel protein biomarkers that could aid in subject selection for pembrolizumab therapy.

Other blood and urine derived Biomarkers: In addition to expression on the tumor tissue, PD-L1 and other tumor-derived proteins can be shed from tumor and released into the blood or urine. Assays such as enzyme-linked immunoassay measure such proteins in serum or urine. Correlation of expression with response to pembrolizumab therapy may identify new approaches for predictive biomarkers in blood or urine, representing a major advance from today's reliance on assessing tumor biomarkers. This research would serve to develop such assays for future clinical use.

4.3 Benefit/Risk

It cannot be guaranteed that subjects in clinical trials will directly benefit from treatment during participation, as clinical trials are designed to provide information about the safety and effectiveness.

Pembrolizumab has been administered in a large number of cancer subjects with a well-characterized safety profile and has received regulatory approval for advanced melanoma, NSCLC, and urothelial carcinoma. Ongoing studies are investigating pembrolizumab as monotherapy or in combination in subjects with mCRPC and SCLC.

Etoposide and cisplatin/carboplatin is the current standard-of-care treatment for small cell cancers of the urothelium and prostate and alternatively docetaxel and carboplatin for neuroendocrine prostate cancer. This regimen is determined from prior clinical responses described in 4.1.4.5.

As the efficacy and safety profile of the pembrolizumab combination therapies has not been well characterized, there is risk that participating subjects may experience new side effects or will not respond to the combinations.

Additional details regarding specific benefits and risks for subjects participating in this clinical trial may be found in the accompanying IB and Informed Consent documents.

5.0 METHODOLOGY

5.1 Study Population

5.1.1 Participant Inclusion Criteria

Participants are eligible to be included in the study only if all of the following criteria apply:

1. Male/female participants who are at least 18 years of age on the day of signing informed consent with histologically confirmed diagnosis of locally advanced or metastatic 1) naïve

small cell cancer of the bladder, urethra, or upper urinary tract, or 2) primary small cell or neuroendocrine prostate cancer will be enrolled in this study.

2. Histological diagnosis of pure or mixed small cell or neuroendocrine cancer by a genitourinary pathologist is sufficient and confirmatory immunohistochemistry is not required.

3. Cohort 1 will include subjects with no prior systemic chemotherapy for locally advanced or metastatic urothelial carcinoma, with the following exception(s):

    a. Platinum-based chemotherapy with recurrence > 12 months from completion of therapy is permitted.

4. Cohort 2 will include subjects with no prior systemic chemotherapy for primary small cell prostate cancer, with the following exception(s):

    a. Platinum-based chemotherapy with recurrence > 12 months from completion of therapy is permitted.

5. Cohort 2 will include subjects with ongoing/prior treatments for mCRPC including:

    a. Prior chemotherapy with 2 other agents is allowed if > 6 months elapsed from last dose (if docetaxel chemotherapy is used more than once for hormone-sensitive and for mCRPC it will be considered 1 therapy).
    b. Ongoing androgen deprivation therapy with up to 2 second-generation hormonal manipulations (e.g. including but not limited to abiraterone acetate and/or enzalutamide). Subjects will remain on androgen deprivation therapy while on study treatment.
    c. Ongoing treatment with for bone metastasis (e.g. denosumab or zoledronic acid) is permitted.
    d. Prior immunotherapy with sipuleucel-T is allowed if completed > 4 weeks prior to trial enrollment.

Male participants:

6. A male participant must agree to use a contraception as detailed in Appendix 3 of this protocol during the treatment period and for at least 120 days after the last dose of pembrolizumab or 180 days after chemotherapy and refrain from donating sperm during this period.

Female participants:

7. A female participant is eligible to participate if she is not pregnant (see Appendix 3), not breastfeeding, and at least one of the following conditions applies:

a. Not a woman of childbearing potential (WOCBP) as defined in Appendix 3 OR
b. A WOCBP who agrees to follow the contraceptive guidance in Appendix 3 during the treatment period and for at least 120 days after the last dose of pembrolizumab or 180 days after chemotherapy.

8. The participant (or legally acceptable representative if applicable) provides written informed consent for the trial.

9. Have measurable disease based on RECIST 1.1, with the following exception(s):

    a. Patients with locally advanced disease defined as muscle-invasive or involving prostatic stroma who are eligible for systemic chemotherapy as standard of care.

    Lesions situated in a previously irradiated area are considered measurable if progression has been demonstrated in such lesions.

10. Have provided archival tumor tissue sample of a tumor lesion not previously irradiated within 6 months of screening. Formalin-fixed, paraffin embedded (FFPE) tissue blocks are preferred to slides. In addition, the availability of fresh frozen tissue is encouraged.

11. Have an Eastern Cooperative Oncology Group (ECOG) performance status of 0 to 1. Evaluation of ECOG is to be performed within 7 days prior to the date of treatment initiation.

12. Have adequate organ function as defined in the following table (Table 1).

    Table 1 Adequate Organ Function Laboratory Values

System	Laboratory Value
Hematological	
Absolute neutrophil count (ANC)	≥1500/μL
Platelets	≥100 000/μL ≥70 000/μL for participants with biopsy proven malignancy infiltrating bone marrow
Hemoglobin	≥9.0 g/dL or ≥5.6 mmol/L[a]
Renal	
Creatinine OR Measured or calculated[b] creatinine clearance (GFR can also be used in place of creatinine or CrCl using a variety of validated GFR calculators)	≤1.5 × ULN OR ≥30 mL/min for participant with creatinine levels >1.5 × institutional ULN OR End-stage renal disease on hemodialysis or peritoneal dialysis

Hepatic	
Total bilirubin	≤1.5 ×ULN OR direct bilirubin ≤ULN for participants with total bilirubin levels >1.5 × ULN
AST (SGOT) and ALT (SGPT)	≤2.5 × ULN (≤5 × ULN for participants with liver metastases)
Coagulation	
International normalized ratio (INR) OR prothrombin time (PT) Activated partial thromboplastin time (aPTT)	≤1.5 × ULN unless participant is receiving anticoagulant therapy as long as PT or aPTT is within therapeutic range of intended use of anticoagulants

ALT (SGPT)=alanine aminotransferase (serum glutamic pyruvic transaminase); AST (SGOT)=aspartate aminotransferase (serum glutamic oxaloacetic transaminase); GFR=glomerular filtration rate; ULN=upper limit of normal.

[a] Criteria must be met without erythropoietin dependency and without packed red blood cell (pRBC) transfusion within last 2 weeks.

[b] Creatinine clearance (CrCl) should be calculated per institutional standard.

Note: This table includes eligibility-defining laboratory value requirements for treatment; laboratory value requirements should be adapted according to local regulations and guidelines for the administration of specific chemotherapies.

5.1.2 Participant Exclusion Criteria

Participants are excluded from the study if any of the following criteria apply:

1. Has disease suitable for local treatment with curative intent.

2. A WOCBP who has a positive urine pregnancy test within 72 hours prior to receiving the first dose of trial medication (see Appendix 3). If the urine test is positive or cannot be confirmed as negative, a serum pregnancy test will be required.

3. Has received prior therapy with an anti-PD-1, anti-PD-L1, or anti-PD-L2 agent or with an agent directed to another stimulatory or co-inhibitory T-cell receptor (e.g. CTLA-4, OX-40, CD137).

4. Has received prior systemic anti-cancer therapy including investigational agents within 4 weeks prior to first dose of trial treatment.

   Note: Participants must have recovered from all AEs due to previous therapies to ≤Grade 1 or baseline. Participants with ≤Grade 2 neuropathy may be eligible.

   Note: If participant received major surgery, they must have recovered adequately from the toxicity and/or complications from the intervention prior to starting study treatment.

5. Has received prior radiotherapy within 2 weeks of start of study treatment. Participants must have recovered from all radiation-related toxicities, not require corticosteroids, and not have had radiation pneumonitis. A 1-week washout is permitted for palliative radiation (≤2 weeks of radiotherapy) to non-CNS disease.

6. Has received a live vaccine within 30 days prior to the first dose of study drug. Examples of live vaccines include, but are not limited to, the following: measles, mumps, rubella, varicella/zoster (chicken pox), yellow fever, rabies, Bacillus Calmette–Guérin (BCG), and typhoid vaccine. Seasonal influenza vaccines for injection are generally killed virus vaccines and are allowed; however, intranasal influenza vaccines (eg, FluMist®) are live attenuated vaccines and are not allowed.

7. Is currently participating in or has participated in a study of an investigational agent or has used an investigational device within 4 weeks prior to the first dose of study treatment.

   Note: Participants who have entered the follow-up phase of an investigational study may participate as long as it has been 4 weeks after the last dose of the previous investigational agent.

8. Has a diagnosis of immunodeficiency or is receiving chronic systemic steroid therapy (in dosing exceeding 10 mg daily of prednisone equivalent) or any other form of immunosuppressive therapy within 7 days prior to the first dose of study drug.

9. Has a known additional malignancy that is progressing or has required active treatment within the past 3 years. Note: Participants with basal cell carcinoma of the skin, squamous cell carcinoma of the skin, or carcinoma in situ (e.g. breast carcinoma, cervical cancer in situ) that have undergone potentially curative therapy are not excluded.

   a. For Cohort 1, a history of prostate cancer that was identified incidentally following cystoprostatectomy for bladder cancer is acceptable provided that the PSA is <0.2.

10. Has known active CNS metastases and/or carcinomatous meningitis. Participants with previously treated brain metastases may participate provided they are radiologically stable, i.e. without evidence of progression for at least 4 weeks by repeat imaging (note that the repeat imaging should be performed during study screening), clinically stable and without requirement of steroid treatment for at least 14 days prior to first dose of study treatment.

11. Has severe hypersensitivity (≥Grade 3) to pembrolizumab and/or any of its excipients.

12. Has active autoimmune disease that has required systemic treatment in the past 2 years (i.e. with use of disease modifying agents, corticosteroids or immunosuppressive drugs). Replacement therapy (eg., thyroxine, insulin, or physiologic corticosteroid replacement therapy for adrenal or pituitary insufficiency, etc.) is not considered a form of systemic treatment.

13. Has a history of (non-infectious) pneumonitis that required steroids or has current pneumonitis.

14. Has an active infection requiring systemic therapy.

15. Has known active Human Immunodeficiency Virus (HIV) infection. However, subjects who are on anti-retroviral therapy, have a viral load < 200 copies/milliliter, and CD4 count > 200/microliter, with a low risk of AIDS-related outcomes will be considered for enrollment.

16. Has a known history of Hepatitis B (defined as Hepatitis B surface antigen [HBsAg] reactive) or known active Hepatitis C virus (defined as HCV RNA [qualitative] is detected) infection. Note: no testing for Hepatitis B and Hepatitis C is required unless mandated by local health authority.

17. Has active TB (Bacillus Tuberculosis).

18. Has a history or current evidence of any condition, therapy, or laboratory abnormality that might confound the results of the study, interfere with the subject's participation for the full duration of the study, or is not in the best interest of the subject to participate, in the opinion of the treating investigator.

19. Has known psychiatric or substance abuse disorders that would interfere with cooperation with the requirements of the trial.

20. Is pregnant or breastfeeding, or expecting to conceive or father children within the projected duration of the study, starting with the screening visit through 120 days after the last dose of trial treatment.

5.1.3 Lifestyle Restrictions

5.1.3.1 Meals and Dietary Restrictions

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

5.1.3.2 Contraception

Pembrolizumab may have adverse effects on a fetus in utero. Chemotherapy including etoposide, cisplatin, and carboplatin are Pregnancy Category D and may have hazardous effects on a fetus in utero. Refer to Appendix 3 for approved methods of contraception.

For this study, male participants will be considered to be of non-reproductive potential if they have azoospermia (whether due to having had a vasectomy or due to an underlying medical condition).

5.1.4 Pregnancy

If a participant inadvertently becomes pregnant while on treatment with pembrolizumab, the participant will be immediately discontinued from study treatment. The site will contact the participant at least monthly and document the participant's status until the pregnancy has been completed or terminated. The outcome of the pregnancy will be reported to Merck within 2 working days if the outcome is a serious adverse experience (eg, death, abortion, congenital anomaly, or other disabling or life-threatening complication to the mother or newborn). The study 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 Merck. If a male participant impregnates his female partner, the study personnel at the site must be informed immediately and the pregnancy must be reported to Merck and followed as described in Section 7.2.2.

5.1.5 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, participants who are breast-feeding are not eligible for enrollment.

5.2 Trial Treatments

The treatment to be used in this trial is outlined below in Table 2.

Table 2 Trial Treatment

Drug	Dose/Potency	Dose Frequency	Route of Administration	Regimen/Treatment Period	Use
Pembrolizumab	200 mg	Q3W	IV infusion	Day 1 of each 3 week cycle	Experimental
Chemotherapy Regimen:					
Etoposide	100 mg/m^2	Q3W	IV infusion	Day 1, 2, 3 of each 3 week cycle	Treatment of small cell cancer
OR					
Docetaxel + Prednisone Dexamethasone	60 mg/m^2 5 mg 8 mg	Q3W	IV infusion Oral IV or Oral	Day 1 of each 3 week cycle/Qd to Bid 8 mg bid day prior and one dose prior to docetaxel	Treatment of neuroendocrine prostate cancer
Plus					
Cisplatin	70-80 mg/m^2	Q3W	IV infusion	Day 1 of each 3 week cycle	Treatment of small cell cancer

Drug	Dose/Potency	Dose Frequency	Route of Administration	Regimen/Treatment Period	Use
OR					
Carboplatin	AUC 4-5	Q3W	IV infusion	Day 1 of each 3 week cycle	Treatment of small cell cancer

5.2.1 Timing of Dose Administration

Trial treatment should be administered on Day 1 of each cycle after all procedures/assessments have been completed as detailed on the Trial Flow Chart (Section 6.0). Pembrolizumab will be administered first, followed by premedication and then the assigned chemotherapy if applicable according to local guidelines and practices. Trial treatment may be administered up to 3 days before or after the scheduled Day 1 of each cycle due to administrative reasons.

5.2.1.1 Pembrolizumab

Pembrolizumab 200 mg will be administered as a 30 minute IV infusion every 3 weeks. 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 -5 minutes and +10 minutes is permitted (i.e., infusion time is 30 minutes: -5 min/+10 min).

The Pharmacy Manual contains specific instructions for the preparation of the pembrolizumab infusion fluid and administration of infusion solution.

5.2.1.2 Etoposide

For subjects receiving etoposide, etoposide will be administered as an IV infusion on Day 1, 2, and 3 of each 3 week cycle according to local guidelines and practices. The first dose of etoposide can be administered on Day 2-3 as per local guidelines.

The use of steroid premedication to reduce hypersensitivity reactions can be used as clinically directed by the treating physician. Premedication with dexamethasone (typically 8 mg PO or IV prior to administration of etoposide) is allowed.

5.2.1.3 Docetaxel

For subjects receiving docetaxel, docetaxel will be administered as an IV infusion on Day 1 of each 3 week cycle according to local guidelines and practices. Docetaxel can be administered on Day 2-3 as per local guidelines.

Premedication with dexamethasone (typically 8 mg PO bid day prior to and 8 mg PO or IV prior to administration of docetaxel) as well as daily dose of prednisone (typically 5 mg qd up to bid)

while on chemotherapy cycles is allowed. After cessation of docetaxel treatment, prednisone should be discontinued.

5.2.1.4 Cisplatin

For subjects receiving cisplatin, cisplatin will be administered as an IV infusion on Day 1 of each 3 week cycle according to local guidelines and practices. Cisplatin can be administered on Day 2-3 as per local guidelines.

The use of steroid premedication to reduce hypersensitivity reactions can be used as clinically directed by the treating physician. Premedication with dexamethasone (typically 8 mg PO or IV prior to administration of cisplatin) is allowed.

5.2.1.5 Carboplatin

Established guidelines will be used as described in 4.1.4.3 for criteria on cisplatin-ineligibility. The treating physician will ultimately make the decision for cisplatin-ineligibility.

For subjects receiving carboplatin, carboplatin will be administered as an IV infusion on Day 1 of each 3 week cycle according to local guidelines and practices. Carboplatin can be administered on Day 2-3 as per local guidelines.

The use of steroid premedication to reduce hypersensitivity reactions can be used as clinically directed by the treating physician. Premedication with dexamethasone (typically 8 mg PO or IV prior to administration of carboplatin) is allowed.

5.2.2 Dose Modification and toxicity management <u>for immune-related AEs associated with pembrolizumab</u>

AEs associated with pembrolizumab exposure may represent an immunologic etiology. These immune-related AEs (irAEs) may occur shortly after the first dose or several months after the last dose of pembrolizumab treatment and may affect more than one body system simultaneously. Therefore, early recognition and initiation of treatment is critical to reduce complications. Based on existing clinical study data, most irAEs were reversible and could be managed with interruptions of pembrolizumab, administration of corticosteroids and/or other supportive care. For suspected irAEs, ensure adequate evaluation to confirm etiology or exclude other causes. Additional procedures or tests such as bronchoscopy, endoscopy, skin biopsy may be included as part of the evaluation. Based on the severity of irAEs, withhold or permanently discontinue pembrolizumab and administer corticosteroids. Dose modification and toxicity management guidelines for irAEs associated with pembrolizumab are provided in Table 3.

Dose interruptions will be allowed, but no dose modifications will be allowed with pembrolizumab. If pembrolizumab is withheld, the entire chemotherapy regimen can be held up to 21 days (+ 3 days) in order to not disrupt the cycle sequence.

Table 3 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
	Grade 4	Permanently discontinue		

				feasible, fluid and electrolytes should be substituted via IV infusion.
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.
	Grade 2	Withhold		• Monitor changes of renal function

Nephritis and Renal dysfunction	Grade 3 or 4	Permanently discontinue	• Administer corticosteroids (prednisone 1-2 mg/kg or equivalent) followed by taper.	
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).

Dose modification and toxicity management of infusion-reactions related to pembrolizumab

Pembrolizumab may cause severe or life threatening infusion-reactions including severe hypersensitivity or anaphylaxis. Signs and symptoms usually develop during or shortly after drug infusion and generally resolve completely within 24 hours of completion of infusion. Dose modification and toxicity management guidelines on pembrolizumab associated infusion reaction are provided in Table 4.

Table 4 Pembrolizumab Infusion Reaction Dose Modification and 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 participant is deemed medically stable in the opinion of the investigator.	None
Grade 2 Requires therapy or infusion interruption but responds promptly to symptomatic treatment (e.g., antihistamines, NSAIDs, narcotics, IV fluids); prophylactic medications indicated for ≤24 hrs	**Stop Infusion.** 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 participant is deemed medically stable in the opinion of the investigator. If symptoms resolve within 1 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 participant should be premedicated for the next scheduled dose. **Participants who develop Grade 2 toxicity despite adequate premedication should be permanently discontinued from further study drug treatment**	Participant 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 analgesic).

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) Grade 4: Life-threatening; pressor or ventilatory support indicated	**Stop Infusion.** Additional appropriate medical therapy may include but is not limited to: Epinephrine** IV fluids Antihistamines NSAIDs Acetaminophen Narcotics Oxygen Pressors Corticosteroids Increase monitoring of vital signs as medically indicated until the participant is deemed medically stable in the opinion of the investigator. Hospitalization may be indicated. **In cases of anaphylaxis, epinephrine should be used immediately. **Participant is permanently discontinued from further study drug treatment.**	No subsequent dosing
Appropriate resuscitation equipment should be available at the bedside and a physician readily available during the period of drug administration. For further information, please refer to the Common Terminology Criteria for Adverse Events v4.0 (CTCAE) at http://ctep.cancer.gov		

Other allowed dose interruption for pembrolizumab

Pembrolizumab may be interrupted for situations other than treatment-related AEs such as medical / surgical events or logistical reasons not related to study therapy. Participants should be placed back on study therapy within 3 weeks of the scheduled interruption, unless otherwise discussed with the Sponsor. The reason for interruption should be documented in the patient's study record.

Subjects with small cell of the urothelium may undergo surgery of primary disease site (e.g. radical cystectomy or nephroureterectomy) as standard-of-care therapy. Pembrolizumab may be withheld to allow recovery and then to continue on study.

Subjects with primary small cell of the prostate may undergo surgery or radiation of primary disease site (e.g. prostate and pelvic lymph nodes) as standard-of-care therapy. Pembrolizumab may be withheld to allow recovery and then to continue on study.

5.2.2.1 Dose modifications for chemotherapy

Dose modifications for etoposide, docetaxel, cisplatin, and/or carboplatin will be implemented according to local guidelines, practices, and approved labeling.

5.2.2.2 Dose interruptions for chemotherapy

If any chemotherapy regimen is withheld secondary to chemotherapy-related toxicity or intolerance, then the entire cycle including study treatment can be delayed up to 21 days (+ 3 days) in order to not disrupt the cycle sequence. If chemotherapy is stopped according to local guidelines, practices, and approved labeling per treating physician's discretion, then the study treatment can continue as monotherapy; provided the subject is deriving benefit from treatment, the subject is in agreement and refusing alternative treatments.

5.2.3 Second Course *

All participants who stop study treatment with stable disease (SD) or better may be eligible for up to an additional 17 cycles (approximately 1 year) of pembrolizumab treatment if they progress after stopping study treatment from the initial treatment phase. This retreatment is termed the Second Course Phase of this study and is only available if the study remains open and the participant meets the following conditions:

Either

- Stopped initial treatment with study treatment after attaining an investigator-determined confirmed CR based on RECIST 1.1, and
    - Was treated with at least 8 cycles of study treatment before discontinuing treatment, and

- Received at least 2 treatments with pembrolizumab beyond the date when the initial CR was declared

OR

- Had SD, PR, or CR and stopped study treatment after completion of 35 administrations (approximately 2 years) of study treatment for reasons other than disease progression or intolerability

AND

- Experienced an investigator-determined radiographic disease progression by RECIST 1.1 or PCWG3 after stopping initial treatment, and
  - No new anticancer treatment was administered after the last dose of study treatment, and
  - The participant meets all of the safety parameters listed in the inclusion criteria and none of the safety parameters listed in the exclusion criteria, and
  - The participant declines additional chemotherapy and investigator feels the Second Course Phase will be beneficial for the patient, and
  - The study is ongoing

An objective response or disease progression that occurs during the Second Course Phase for a participant will not be counted as an event for the primary analysis of either endpoint in this study.

**Note: patients must have measurable disease at the start of protocol treatment to be eligible for this provision by RECIST 1.1 or PCWG3 for bone only metastases.*

5.3 Randomization or Treatment Allocation

This is a non-randomized open label study. The Sponsor, investigator, and subject will know the treatment administered.

5.4 Stratification

No stratification based on age, gender, or other characteristics will be used in this trial.

5.5 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 one of these or other medications or vaccinations specifically prohibited during the trial, discontinuation from trial therapy or vaccination may be required. The final decision on any supportive therapy or vaccination rests with the investigator and/or the participants' primary physician.

5.5.1 Acceptable Concomitant Medications

All treatments that the investigator considers necessary for a participant's welfare may be administered at the discretion of the investigator in keeping with the community standards of medical care. This includes growth factors used in conjunction with chemotherapy. 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 28 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 as defined in Section 7.2.

5.5.2 Prohibited Concomitant Medications

Participants 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, to the brain, or to the prostate gland and pelvic lymph nodes for consolidation following completion of initial cycles of chemotherapy may be allowed at the investigator's discretion.
- Live vaccines within 30 days prior to the first dose of study treatment and while participating in the study. Examples of live vaccines include, but are not limited to, the following: measles, mumps, rubella, varicella/zoster, yellow fever, rabies, BCG, and typhoid vaccine. Seasonal influenza vaccines for injection are generally killed virus vaccines and are allowed; however, intranasal influenza vaccines (eg, FluMist®) 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 or as standard-of-care in combination with chemotherapy. The use of physiologic doses of corticosteroids may be approved after consultation with the Sponsor.

Participants who, in the assessment by the investigator, require the use of any of the aforementioned treatments for clinical management should be removed from the study. All treatments that the Investigator considers necessary for a participant's welfare may be

administered at the discretion of the Investigator in keeping with the community standards of medical care.

Medications or vaccinations specifically prohibited in the exclusion criteria are not allowed during the ongoing study. If there is a clinical indication for any medication or vaccination specifically prohibited during the study, discontinuation from study therapy or vaccination may be required. The final decision on any supportive therapy or vaccination rests with the investigator and/or the participant's primary physician. However, the decision to continue the participant on study treatment requires the mutual agreement of the investigator, the Sponsor and the participant.

There are no prohibited therapies during the Post-Treatment Follow-up Phase.

5.5.3 Rescue Medications & Supportive Care

Participants should receive appropriate supportive care measures as deemed necessary by the treating investigator. Suggested supportive care measures for the management of AEs with potential immunologic etiology are outlined along with the dose modification guidelines in Section 5.2.2, [Table 3]. Where appropriate, these guidelines include the use of oral or IV 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 Investigator determines the events to be related to pembrolizumab.

Note: If after the evaluation of the event, it is determined not to be related to pembrolizumab, the Investigator does not need to follow the treatment guidance. Refer to [Table 3] in Section 5.2.2 for guidelines regarding dose modification and supportive care.

It may be necessary to perform conditional procedures such as bronchoscopy, endoscopy, or skin photography as part of evaluation of the event.

5.6 Participant Withdrawal/Discontinuation Criteria

Participants may discontinue study treatment at any time for any reason or be dropped from the study treatment at the discretion of the investigator should any untoward effect occur. In addition, a participant may be discontinued from study treatment by the investigator or the Sponsor if study treatment is inappropriate, the trial plan is violated, or for administrative and/or other safety reasons. Specific details regarding procedures to be performed at study treatment discontinuation are provided in Section 7.1.4 – Other Procedures.

A participant must be discontinued from study treatment but continue to be monitored in the study for any of the following reasons:

- The participant or participant's legally acceptable representative requests to discontinue study treatment
- Confirmed radiographic disease progression outlined in Section 7.1.2.6
- Any progression or recurrence of any malignancy, or any occurrence of another malignancy that requires active treatment
- Unacceptable adverse experiences as described in Section 5.2.2.
- The participant has a medical condition or personal circumstance which, in the opinion of the investigator and/or sponsor, placed the participant at unnecessary risk from continued administration of study treatment.
- The participant has a confirmed positive serum pregnancy test
- Noncompliance with study treatment or procedure requirements
- Recurrent Grade 2 pneumonitis
- Discontinuation of treatment may be considered for participants who have attained a confirmed complete response (CR) and have been treated for at least 8 cycles (at least 24 weeks), receiving at least 4 cycles of the combination including 2 doses of pembrolizumab beyond the date when the initial CR was declared. These participants may be eligible for second course treatment described in Section 5.2.3.
- The participant is lost to follow-up
- Completion of 35 treatments (approximately 2 years) with pembrolizumab

  Note: The number of treatments is calculated starting with the first dose. Participants who stop the combination or pembrolizumab after receiving 35 doses may be eligible for retreatment if they progress after stopping study treatment provided they meet the requirements detailed in Section 5.2.3. Participants may be re-treated in the Second Course Phase (Retreatment) for up to an additional 17 cycles (approximately 1 year).

- Administrative reasons

5.7 Participant Replacement Strategy

Subject participants will not be replaced if they started study treatment.

5.8 Clinical Criteria for Early Trial Termination

Early trial termination will be the result of the criteria specified below:

1. Quality or quantity of data recording is inaccurate or incomplete
2. Poor adherence to protocol and regulatory requirements

3. Incidence or severity of adverse drug reaction in this or other studies indicates a potential health hazard to participants

4. Plans to modify or discontinue the development of the study drug

In the event of Merck decision to no longer supply study drug, ample notification will be provided so that appropriate adjustments to participant treatment can be made.

6.0 TRIAL FLOW CHART

6.1 Study Flow Chart

Trial Period:	Screening Phase	Treatment Cycles[a]								End of Treatment	Post-Treatment		
						To be repeated beyond 8 cycles							
Treatment Cycle/Title:	Study Screening	1	2	3	4	5	6	7	8	Discon	Safety Follow-up	Follow Up Visits[b]	Survival Follow-Up
Scheduling Window (Days):	-28 to -1		± 3	± 3	± 3	± 3	± 3	± 3	± 3	At time of Discon	30 days post discon (± 3)	Every 12 weeks post discon (± 3)	Every 12 weeks (± 14 days)
Administrative Procedures													
Informed Consent	X												
Inclusion/Exclusion Criteria	X												
Demographics and Medical History	X												
Prior and Concomitant Medication Review	X	X	X	X	X	X	X	X	X	X	X		
Trial Treatment Administration[c]		X	X	X	X	X	X	X	X				
Post-study anticancer therapy status											X		X
Survival Status													X
Clinical Procedures/Assessments													
Review Adverse Events	X	X	X	X	X	X	X	X	X	X	X	X	
Full Physical Examination	X												
Directed Physical Examination		X	X	X	X	X	X	X	X	X	X	X	
Vital Signs and Weight	X	X	X	X	X	X	X	X	X	X	X	X	
ECOG Performance Status	X	X	X	X	X	X	X	X	X	X	X	X	
Laboratory Procedures/Assessments: analysis performed by LOCAL laboratory													
Pregnancy Test – Urine or Serum β-HCG	X												
PT/INR and aPTT	X												
CBC with Differential	X		X	X	X	X	X	X	X	X	X	X	

Trial Period:	Screening Phase	Treatment Cycles[a]								End of Treatment	Post-Treatment		
						To be repeated beyond 8 cycles							
Treatment Cycle/Title:	Study Screening	1	2	3	4	5	6	7	8	Discon	Safety Follow-up	Follow Up Visits[b]	Survival Follow-Up
Scheduling Window (Days):	-28 to -1		± 3	± 3	± 3	± 3	± 3	± 3	± 3	At time of Discon	30 days post discon (± 3)	Every 12 weeks post discon (± 3)	Every 12 weeks (± 14 days)
Comprehensive Serum Chemistry Panel	X		X	X	X	X	X	X	X	X	X	X	
TSH with Reflex Free T3 and T4	X		X		X		X		X	X	X		
LDH	X		X	X	X	X	X	X	X	X	X		
Lipase	X								X	X	X		
Urinalysis	X										X		
Efficacy Measurements													
Tumor Imaging[d]	X				X				X	X		X	
PSA[e]	X		X		X		X		X	X		X	
Tumor Biopsies/Archival Tissue Collection/Correlative Studies Blood													
Archival Tissue Collection[f]	X												
Correlative Studies Blood Collection		X		X		X		X		X			

[a]In general, assessments/procedures are to be performed on Day 1 and prior to the first dose of treatment for each cycle unless otherwise specified. Day 1 is the preferred start day of treatment administration for all chemotherapies; however these chemotherapy treatments may be given on Day 2-3 if required by local guidelines. Treatment cycles are 3 weeks; however, the treatment cycle interval may be increased due to toxicity according to the dose modification guidelines provided in Section 5.2.1.2. If the interval is increased, all procedures except imaging should be performed based on the new dosing schedule. Imaging should be performed initially at 9 weeks (63 days ±14) from treatment initiation and every 12 weeks (84 days ±14) based on previous scan date thereafter, regardless of any treatment delays.

[b]Subjects who discontinue study therapy without documented disease progression should continue monitoring disease status every 12 weeks (84 days ±14) for approximately 2 years until the start of new anti-cancer treatment, documented disease progression, death, or the end of the study, whichever comes first.

[c]Trial treatment will be given first, followed by premedication and then the assigned standard of care chemotherapy.

[d]Imaging should be performed initially at 9 weeks (63 days ±14) from treatment initiation and every 12 weeks (84 days ±14) thereafter, based on date of previous scan.

[e] For Cohort 2 only

Trial Period:	**Screening Phase**	**Treatment Cycles[a]**								**End of Treatment**	**Post-Treatment**		
						To be repeated beyond 8 cycles							
Treatment Cycle/Title:	Study Screening	1	2	3	4	5	6	7	8	Discon	Safety Follow-up	Follow Up Visits[b]	Survival Follow-Up
Scheduling Window (Days):	-28 to -1		± 3	± 3	± 3	± 3	± 3	± 3	± 3	At time of Discon	30 days post discon (± 3)	Every 12 weeks post discon (± 3)	Every 12 weeks (± 14 days)
	[f]Additional tissue may be obtained in subjects who undergo surgery/radiation or at time of progression.												

7.0 TRIAL PROCEDURES

7.1 Trial Procedures

The Trial Flow Chart - Section 6.0 summarizes the trial procedures to be performed at each visit. Individual trial procedures are described in detail below. It may be necessary to perform these procedures at unscheduled time points if deemed clinically necessary by the investigator.

Furthermore, additional evaluations/testing may be deemed necessary by the Sponsor and/or Merck for reasons related to participant safety. In some cases, such evaluation/testing may be potentially sensitive in nature (e.g., HIV, Hepatitis C, etc.), and thus local regulations may require that additional informed consent be obtained from the participant. In these cases, such evaluations/testing will be performed in accordance with those regulations.

7.1.1 Administrative Procedures

7.1.1.1 Informed Consent

The Investigator must obtain documented consent from each potential participant prior to participating in a clinical trial.

7.1.1.1.1 General Informed Consent

Consent must be documented by the participant's dated signature or by the participant's legally acceptable representative's dated signature on a consent form along with the dated signature of the person conducting the consent discussion.

A copy of the signed and dated consent form should be given to the participant before participation in the trial.

The initial informed consent form, any subsequent revised written informed consent form and any written information provided to the participant must receive the IRB/ERC's approval/favorable opinion in advance of use. The participant or his/her legally acceptable representative should be informed in a timely manner if new information becomes available that may be relevant to the participant's willingness to continue participation in the trial. The communication of this information will be provided and documented via a revised consent form or addendum to the original consent form that captures the participant's dated signature or by the participant's legally acceptable representative's dated signature.

Specifics about the trial and the trial population will be added to the consent form template at the protocol level.

The informed consent will adhere to IRB/ERC requirements, applicable laws and regulations and Sponsor requirements.

7.1.1.2 Inclusion/Exclusion Criteria

All inclusion and exclusion criteria will be reviewed by the investigator or qualified designee to ensure that the participant qualifies for the trial.

7.1.1.3 Medical History

A medical history will be obtained by the investigator or qualified designee. Medical history will include all active conditions, and any condition diagnosed within the prior 10 years that are considered to be clinically significant by the Investigator. Details regarding the disease for which the participant has enrolled in this study will be recorded separately and not listed as medical history.

7.1.1.4 Prior and Concomitant Medications Review

7.1.1.4.1 Prior Medications

The investigator or qualified designee will review prior medication use, including any protocol-specified washout requirement, and record prior medication taken by the participant within 28 days before starting the trial. Treatment for the disease for which the participant has enrolled in this study will be recorded separately and not listed as a prior medication.

7.1.1.4.2 Concomitant Medications

The investigator or qualified designee will record medication, if any, taken by the participant during the trial. All medications related to reportable SAEs and ECIs should be recorded as defined in Section 7.2.

7.1.1.5 Disease Details and Treatments

7.1.1.5.1 Disease Details

The investigator or qualified designee will obtain prior and current details regarding disease status.

7.1.1.5.2 Prior Treatment Details

The investigator or qualified designee will review all prior cancer treatments including systemic treatments, radiation and surgeries.

7.1.1.5.3 Subsequent Anti-Cancer Therapy Status

The investigator or qualified designee will review all new anti-neoplastic therapy initiated after the last dose of trial treatment. If a participant initiates a new anti-cancer therapy within 30 days after the last dose of trial treatment, the 30-day Safety Follow-up visit must occur before the first dose of the new therapy. Once new anti-cancer therapy has been initiated the participant will move into survival follow-up.

7.1.1.6 Assignment of Screening Number

Each subject will be assigned only one screening number. Screening numbers must not be re-used for different subjects. Any subject who is screened multiple times will retain the original screening number assigned at the initial screening visit.

7.1.1.7 Trial Compliance (Medication/Diet/Activity/Other)

Interruptions from the protocol specified treatment plan for greater than 18 weeks between pembrolizumab doses due to toxicity will require written documentation on subject management.

7.1.2 Clinical Procedures/Assessments

7.1.2.1 Adverse Event (AE) Monitoring

The investigator or qualified designee will assess each participant to evaluate for potential new or worsening AEs as specified in the Trial Flow Chart and more frequently if clinically indicated. Adverse experiences will be graded and recorded throughout the study and during the follow-up period according to NCI CTCAE Version 4.0 (see Appendix 2). Toxicities will be characterized in terms regarding seriousness, causality, toxicity grading, and action taken with regard to trial treatment.

Please refer to section 7.2 for detailed information regarding the assessment and recording of AEs.

7.1.2.2 Full Physical Exam

The investigator or qualified designee will perform a complete physical exam during the screening period. Clinically significant abnormal findings should be recorded as medical history. A full physical exam should be performed during screening,

7.1.2.3 Directed Physical Exam

For cycles that do not require a full physical exam per the Trial Flow Chart, the investigator or qualified designee will perform a directed physical exam as clinically indicated prior to trial treatment administration.

7.1.2.4 Vital Signs

The investigator or qualified designee will take vital signs at screening, prior to the administration of each dose of trial treatment and at treatment discontinuation as specified in the Trial Flow Chart (Section 6.0). Vital signs should include temperature, pulse, respiratory rate, weight and blood pressure. Height will be measured at screening only.

7.1.2.5 Eastern Cooperative Oncology Group (ECOG) Performance Scale

The investigator or qualified designee will assess ECOG status (see Appendix 1) at screening, prior to the administration of each dose of trial treatment and discontinuation of trial treatment as specified in the Trial Flow Chart.

7.1.2.6 Tumor Imaging and Assessment of Disease

Tumor imaging is strongly preferred to be acquired by computed tomography (CT). For the abdomen and pelvis, contrast-enhanced magnetic resonance imaging (MRI) may be used when CT with iodinated contrast is contraindicated, or when local practice mandates it. CT urogram is an acceptable substitute for CT abdomen/pelvis. MRI is the strongly preferred modality for imaging the brain. The same imaging technique regarding modality and the use of contrast should be used in a participant throughout the study to optimize the reproducibility of the assessment of existing and new tumor burden and improve the accuracy of the assessment of response or progression based on imaging.

For Cohort 1, imaging will include the chest, abdomen, and pelvis. For Cohort 2, imaging will include the chest, abdomen, and pelvis and a radionuclide bone scan.

Local review of imaging (investigator assessment with site radiology reading) will be used for subject management and evaluation of response to treatment.

7.1.2.6.1 Initial Tumor Imaging

Initial tumor imaging at Screening must be performed 28 days prior to the date of treatment initiation. The site study team must review screening images to confirm the participant has measurable disease per RECIST 1.1. Scans performed as part of routine clinical management are acceptable for use as screening tumor imaging if they are of diagnostic quality and performed within 28 days prior to date of treatment initiation.

Although RECIST 1.1 references to a maximum of 5 target lesions in total and 2 per organ, this study allows a maximum of 10 target lesions in total and 5 per organ, if clinically relevant to enable a broader sampling of tumor burden.

Brain imaging, if performed to document the stability of existing metastases, should be by MRI if possible. If MRI is medically contraindicated, CT with contrast is an acceptable alternative.

Patients with locally advanced disease will not be required to have measurable disease by RECIST 1.1. These patients will be eligible for extirpative surgery as discussed in 5.2.2 for dose interruption.

7.1.2.6.1 Tumor Imaging During the Study

The first on-study imaging assessment should be performed within 63 days (±14 days) from the date of treatment initiation. Subsequent tumor imaging (regular scheduled imaging) should

be performed every 12 weeks (84 days ±14 days) thereafter based on the date of the previous scan, including confirmatory scans. Imaging timing should follow calendar days and should not be adjusted for delays in cycle starts. Imaging should continue to be performed until disease progression is identified by the Investigator.

Objective response should be confirmed by a repeat imaging assessment. Tumor imaging to confirm partial response (PR) or complete response (CR) should be performed at least 4 weeks after the first indication of a response is observed. Participants will then return to regular scheduled imaging.

For patients with locally advanced disease without measurable disease by RECIST 1.1, response to treatment including PR or CR will be determined by pathologic staging following extirpative surgery. Disease progression will be defined as a new measurable lesion by RECIST 1.1.

Per iRECIST (Section 9.2.1.6), disease progression should be confirmed by the site over 4 weeks after first radiologic evidence of progressive disease (PD) in clinically stable participants. Participants who have unconfirmed disease progression may continue on treatment at the discretion of the Investigator until progression is confirmed by the site provided they have met the conditions detailed in Section 9.2.1.6. Participants who receive confirmatory imaging may resume tumor imaging at the subsequent scheduled imaging time point, if clinically stable. Participants who have confirmed disease progression by iRECIST, as assessed by the site, will discontinue study treatment. Exceptions are detailed in Section 9.2.1.6.

Radiographic progression for bone lesions will be determined as described in the consensus guidelines of the PCWG3. Radiographic progression of bone lesions will be defined as the appearance of ≥2 new bone lesions on radionuclide bone scan. Progression in bone if unaccompanied by soft tissue progression, requires a second radionuclide bone scan ≥4 weeks later. Progression is confirmed to have occurred if the confirmation bone scan shows ≥2 additional new lesions.

If a subject with radiographic progression is clinically stable or clinically improved, and there is no further increase in the tumor dimensions at the confirmatory scan, an exception may be considered to continue treatment upon consultation with the Sponsor. Clinically stable subjects should also have at the confirmatory scan no further increase in the target lesions, no unequivocal increase in non-target lesions and no additional new lesions develop (non-worsening progressive disease) to continue study treatment.

7.1.2.6.2 End of Treatment and Follow-up Tumor Imaging

In participants who discontinue study treatment, tumor imaging should be performed at the time of treatment discontinuation (±4 week window). If previous imaging was obtained within 4 weeks prior to the date of discontinuation, then imaging at treatment discontinuation is not mandatory. In participants who discontinue study treatment due to documented disease

progression and the Investigator elects not to implement iRECIST, this is the final required tumor imaging.

In participants who discontinue study treatment without documented disease progression, every effort should be made to continue monitoring their disease status by tumor imaging using the same imaging schedule used while on treatment. Imaging should continue every 12 weeks (84 days ±14 days, based on the date of the previous scan) for approximately 2 years to monitor disease status until the start of a new anticancer treatment, disease progression, death, withdrawal of consent, or the end of the study, whichever occurs first.

7.1.2.6.3 Second Course (Retreatment) Tumor Imaging

Tumor imaging must be performed within 28 days prior to restarting treatment with pembrolizumab. Local reading (Investigator assessment with site radiology reading) will be used to determine eligibility.

The first on-study imaging assessment should be performed every 12 weeks (84 days ±14 days, based on the date of the previous scan) after the restart of treatment.

Per RECIST 1.1 (Section 9.1.2.6), if tumor imaging shows initial PD, tumor assessment should be repeated 4 to 8 weeks later in order to confirm PD with the option of continuing treatment while awaiting radiologic confirmation of progression. Participants who obtain confirmatory imaging do not need to undergo scheduled tumor imaging if it is less than 4 weeks later and may wait until the next scheduled imaging time point, if clinically stable.

Imaging should continue to be performed until disease progression, the start of a new anticancer treatment, withdrawal of consent, death, or notification by the Sponsor, whichever occurs first. Disease progression may be confirmed 4 to 8 weeks after the first tumor imaging indicating PD, by the Investigator using iRECIST, in clinically stable participants.

In participants who discontinue study treatment, tumor imaging should be performed at the time of treatment discontinuation (±4 week window). If previous imaging was obtained within 4 weeks prior to the date of discontinuation, then imaging at treatment discontinuation is not mandatory. In participants who discontinue study treatment due to documented disease progression, this is the final required tumor imaging.

In participants who discontinue study treatment without documented disease progression, every effort should be made to continue monitoring their disease status by radiologic imaging every 12 weeks (84 days ±14 days, based on the date of the previous scan) until either the start of a new anticancer treatment, disease progression, death, or the end of the study, whichever occurs first.

7.1.2.6.4 RECIST 1.1 Assessment of Disease

RECIST 1.1 will be used as the primary measure for assessment of tumor response, date of disease progression, and as a basis for all protocol guidelines related to disease status (eg, discontinuation of study treatment). Although RECIST 1.1 references a maximum of 5 target

lesions in total and 2 per organ, the Sponsor allows a maximum of 10 target lesions in total and 5 per organ, if clinically relevant to enable a broader sampling of tumor burden.

Patients with locally advanced disease will not be required to have measurable disease by RECIST 1.1. These patients will be eligible for extirpative surgery as discussed in 5.2.2 for dose interruption. Response to treatment including PR or CR will be determined by pathologic staging following extirpative surgery. Disease progression will be defined as a new measurable lesion by RECIST 1.1.

7.1.2.6.5 iRECIST Assessment of Disease

iRECIST is based on RECIST 1.1, but adapted to account for the unique tumor response seen with immunotherapeutic drugs. When clinically stable, participants should not be discontinued until progression is confirmed by the Investigator, working with local radiology, according to the rules below. This allowance to continue treatment despite initial radiologic PD takes into account the observation that some participants can have a transient tumor flare in the first few months after the start of immunotherapy, and then experience subsequent disease response.

A description of the adaptations and iRECIST process is provided in Appendix 4, with additional detail in the iRECIST publication [55]. iRECIST will be used by the Investigator to assess tumor response and progression, and make treatment decisions.

7.1.2.6.6 PCWG3 Assessment of Progression

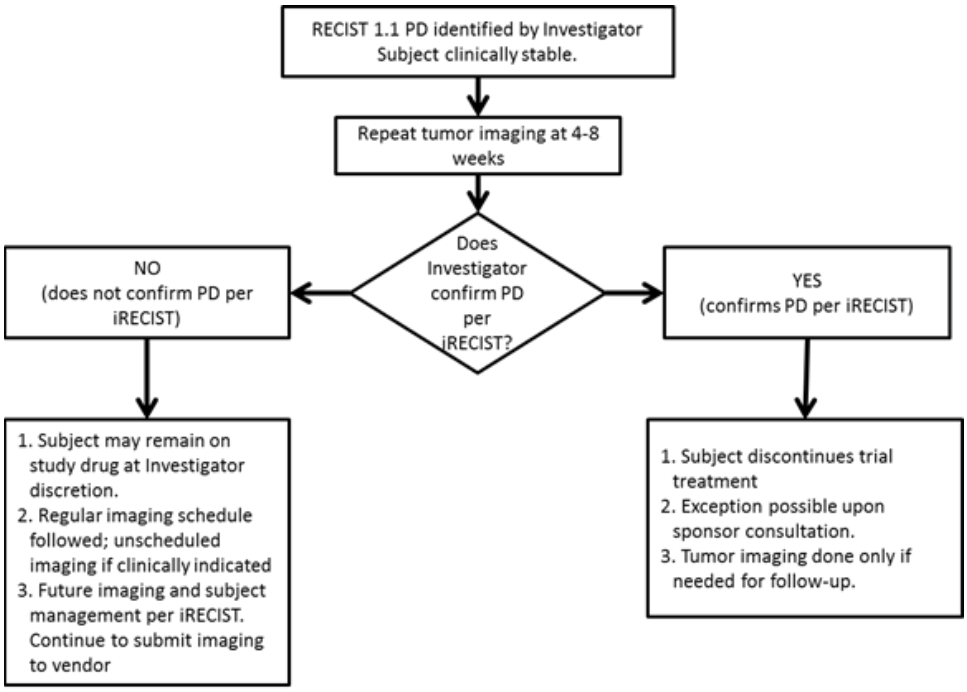
Radiographic progression for metastatic prostate cancer in bone only disease is described in the consensus guidelines of the PCWG3 (REF). Pseudoprogression in the absence of symptoms or other signs of progression are excluded. Radiographic progression of bone lesions will be defined as the appearance of ≥2 new bone lesions on first radionuclide bone scan with at least 2 additional lesions on the next confirmatory scan ≥4 weeks later. Date of progression is the date of the first post-treatment scan.

Table 5 Imaging and Treatment after First Radiologic Evidence of Progressive Disease

	Clinically Stable		**Clinically Unstable**	
	Imaging	**Treatment**	**Imaging**	**Treatment**
First radiologic evidence of PD by RECIST 1.1	Repeat imaging at 4 to 8 weeks to confirm PD.	May continue study treatment at the Investigator's discretion while awaiting confirmatory tumor imaging by site by iRECIST.	Repeat imaging at 4 to 8 weeks to confirm PD per Investigator's discretion only.	Discontinue treatment
Repeat tumor imaging confirms PD (iCPD) by iRECIST per Investigator assessment	No additional imaging required.	Discontinue treatment (exception is possible upon consultation with Sponsor).	No additional imaging required.	Not applicable
Repeat tumor imaging shows iUPD by iRECIST per Investigator assessment	Repeat imaging at 4 to 8 weeks to confirm PD. May occur at next regularly scheduled imaging visit.	Continue study treatment at the Investigator's discretion.	Repeat imaging at 4 to 8 weeks to confirm PD per Investigator's discretion only.	Discontinue treatment
Repeat tumor imaging shows iSD, iPR, or iCR by iRECIST per Investigator assessment.	Continue regularly scheduled imaging assessments.	Continue study treatment at the Investigator's discretion.	Continue regularly scheduled imaging assessments.	May restart study treatment if condition has improved and/or clinically stable per Investigator's discretion. Next tumor image should occur according to the regular imaging schedule.

iCPD = iRECIST confirmed progressive disease; iCR = iRECIST complete response; iRECIST = modified Response Evaluation Criteria in Solid Tumors 1.1 for immune-based therapeutics; iSD = iRECIST stable disease; iUPD = iRECIST unconfirmed progressive disease; PD = progressive disease; RECIST 1.1 = Response Evaluation Criteria in Solid Tumors 1.1.

Figure 1: Imaging and Treatment for Clinically Stable Participants after First Radiologic Evidence of PD Assessed by the Investigator



7.1.2.7 Tumor Tissue Collection and Correlative Studies Blood Sampling

7.1.2.7.1 Tumor Tissue Collection

An archival formalin-fixed paraffin-embedded (FFPE) tumor tissue within 6 months of screening is required. Tissue may also be obtained if the patient undergoes surgery or radiation if indicated as standard-of-care. Subjects will undergo a research biopsy to collect tissue at the time of disease progression.

Although inclusion in this study is not contingent on PD-L1 status, tumor tissue will be tested to evaluate PD-L1 status.

Sample collection, storage and shipment instructions will be in the Procedures Manual. Leftover tissue will be stored at the end of the study for future biomedical research (FBR) if the subject consents to FBR. This may include but not limited to exome sequencing, RNA sequencing, and immunohistochemistry.

7.1.2.7.2 Blood Collection for RNA Analysis, Plasma and Serum Biomarker Analyses

Blood should be collected pre-dose every other cycle starting at Cycle 1 and at time of treatment discontinuation. Analysis may include neuroendocrine markers such as serum CEA, chromogranin, neuron-specific enolase, and synaptophysin levels that may be part of standard of care. Leftover samples will be kept for future biomedical research if the subject signs the FBR consent.

Sample collection, storage and shipment instructions will be in the Procedures Manual.

7.1.2.7.3 Blood Collection for Circulating Tumor DNA

Blood for circulating tumor DNA (ctDNA) will be collected pre-dose every other cycle starting at Cycle 1 and at time of treatment discontinuation. Analysis may include but not limited to biomarker analysis and exome or gene panel sequencing. Leftover samples may be kept for future biomedical research if the subject signs the FBR consent.

Samples will be placed in appropriate tubes and collection, storage, and shipment instructions will be in the Procedures Manual.

7.1.2.7.4 Blood Collection for CTCs

Blood for CTC will be collected pre-dose every other cycle starting at Cycle 1 and at time of treatment discontinuation. Analysis may include but not limited to cell enumeration, expression of PD-L1, and analyses of cellular heterogeneity by single cell RNA sequencing. Leftover samples may be kept for future biomedical research if the subject signs the FBR consent.

Samples will be placed in appropriate tubes and collection, storage, and shipment instructions will be in the Procedures Manual.

7.1.3 Laboratory Procedures/Assessments

Laboratory tests for hematology, chemistry, urinalysis, and others are specified in Table 6.

Table 6 Laboratory Tests

Hematology	Chemistry	Urinalysis	Other
Hematocrit	Albumin	Blood	Serum β-human chorionic gonadotropin†
Hemoglobin	Alkaline phosphatase	Glucose	(β-hCG)†
Platelet count	Alanine aminotransferase (ALT)	Protein	PT (INR)
WBC (total and differential)	Aspartate aminotransferase (AST)	Specific gravity	aPTT
Red Blood Cell Count	Lactate dehydrogenase (LDH)	Microscopic exam *(If abnormal)*	Thyroid stimulating hormone (TSH)
Absolute Neutrophil Count	Carbon Dioxide	results are noted	Total triiodothyronine (T3) (reflex)
Absolute Lymphocyte Count	*(CO_2 or biocarbonate)*	Urine pregnancy test †	Free thyroxine (T4) (reflex)
	Uric Acid		Lactate Dehydrogenase (LDH)
	Calcium		Lipase
	Chloride		Prostate Specific Antigen (PSA) – Cohort 2 only
	Glucose		
	Phosphorus		Blood for correlative studies
	Potassium		
	Sodium		
	Magnesium		
	Total Bilirubin		
	Direct Bilirubin *(If total bilirubin is elevated above the upper limit of normal)*		
	Total protein		
	Blood Urea Nitrogen		

† Perform on women of childbearing potential only. If urine pregnancy results cannot be confirmed as negative, a serum pregnancy test will be required.

Laboratory tests for screening or entry into the Second Course Phase should be performed within 28 days prior to the first dose of treatment. After Cycle 1, pre-dose laboratory procedures can be conducted up to 72 hours prior to dosing. Results must be reviewed by the investigator or qualified designee and found to be acceptable prior to each dose of trial treatment.

7.1.4 Other Procedures

7.1.4.1 Withdrawal/Discontinuation

When a participant discontinues/withdraws prior to trial completion, all applicable activities scheduled for the final trial visit should be performed at the time of discontinuation. Any adverse events which are present at the time of discontinuation/withdrawal should be followed in accordance with the safety requirements outlined in Section 7.2 - Assessing and Recording Adverse Events. Participants who a) attain a CR or b) complete 35 doses with pembrolizumab may discontinue treatment with the option of restarting treatment if they meet the criteria specified in Section 5.2.3. After discontinuing treatment following assessment of CR, these participants should return to the site for a Safety Follow-up Visit (described in Section 7.1.5.3.1) and then proceed to the Follow-Up Period of the study (described in Section 7.1.5.3.2).

7.1.5 Visit Requirements

Visit requirements are outlined in Section 6.0 - Trial Flow Chart. Specific procedure-related details are provided above in Section 7.1 - Trial Procedures.

7.1.5.1 Screening

7.1.5.1.1 Screening Period

Approximately 28 days prior to enrollment, potential subjects will be evaluated to determine that they fulfill the entry requirements.

Subjects must sign the main trial consent prior to submitting existing tissue samples and/or undergoing a new biopsy. Results of a test performed prior to the subject signing consent as part of routine clinical management are acceptable in lieu of a screening test if performed within the specified time frame. Screening procedures are to be completed within 28 days prior to the first dose of trial treatment, except for the following:

- Laboratory tests are to be performed within 2 weeks of trial initiation.
- For women of reproductive potential, a urine pregnancy test will be performed within 72 hours prior to the first dose of trial treatment. If urine pregnancy results cannot be confirmed as negative, a serum pregnancy test will be required (performed by the local trial site laboratory).

Subjects may be rescreened after initially failing to meet the inclusion/exclusion criteria.

Results from assessments performed during the initial screening period are acceptable in lieu of a repeat screening test if performed within the specified time frame and the inclusion/exclusion criteria is met. The subject identification card will be updated with the screening number.

7.1.5.2 Treatment Period

Visit requirements are outlined in Section 6.0 - Trial Flow Chart.

7.1.5.3 Post-Treatment Visits

The discontinuation visit should be conducted approximately within 28 days ± 7 days after the last dose of trial treatment or before the initiation of a new anti-neoplastic treatment, whichever comes first.

7.1.5.3.1 Safety Follow-Up Visit

The mandatory Safety Follow-Up Visit should be conducted approximately 30 days after the last dose of study treatment or before the initiation of a new anti-cancer treatment, whichever comes first. All AEs that occur prior to the Safety Follow-Up Visit should be recorded. Participants with an AE of Grade > 1 will be followed until the resolution of the AE to Grade 0-1 or until the beginning of a new anti-cancer therapy, whichever occurs first. SAEs that occur within 90 days of the end of treatment or before initiation of a new anti-cancer treatment should also be followed and recorded. Participants who are eligible for retreatment with pembrolizumab (as described in Section 5.2.3) may have up to two safety follow-up visits, one after the Initial Treatment Period and one after the Second Course Treatment.

7.1.5.3.2 Follow-up Visits

Participants who discontinue study treatment for a reason other than disease progression will move into the Follow-Up Phase and should be assessed every 12 weeks (84 ± 14 days, based on the date of the previous scan) by radiologic imaging to monitor disease status for 2 years. Every effort should be made to collect information regarding disease status until the start of new anti-cancer therapy, disease progression, death, end of the study or if the participant begins retreatment with pembrolizumab as detailed in Section 5.2.3. Information regarding post-study anti-cancer treatment will be collected if new treatment is initiated.

Participants who are eligible to receive retreatment with pembrolizumab according to the criteria in Section 5.2.3 will move from the follow-up phase to the Second Course Phase when they experience disease progression.

7.1.5.3.3 Survival Follow-up

Participants who experience confirmed disease progression or start a new anticancer therapy, will move into the Survival Follow-Up Phase and should be contacted by telephone every 12 weeks to assess for survival status until death, withdrawal of consent, or the end of the trial, whichever occurs first.

7.2 Assessing and Recording Adverse Events

An adverse event is defined as any untoward medical occurrence in a patient or clinical investigation participant administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment. An adverse event can therefore be any unfavorable and unintended sign, symptom, or disease temporally associated with the use of a medicinal product or protocol-specified procedure, whether or not considered related to the medicinal product or protocol-specified procedure. Any worsening (i.e., any clinically significant adverse change in frequency and/or intensity) of a preexisting condition that is temporally associated with the use of the Merck's product, is also an adverse event.

All laboratory findings will be reviewed by an Investigator. All laboratory results outside the reference range will be categorized as clinically significant or not clinically significant. Only clinically significant abnormal results will be recorded as an AE.

Changes resulting from normal growth and development that do not vary significantly in frequency or severity from expected levels are not to be considered adverse events. Examples of this may include, but are not limited to, teething, typical crying in infants and children and onset of menses or menopause occurring at a physiologically appropriate time.

Merck product includes any pharmaceutical product, biological product, device, diagnostic agent or protocol-specified procedure, whether investigational (including placebo or active comparator medication) or marketed, manufactured by, licensed by, provided by or distributed by Merck for human use.

Adverse events may occur during the course of the use of Merck product in clinical trials, or as prescribed in clinical practice, from overdose (whether accidental or intentional), from abuse and from withdrawal.

● All AEs from the time of initial consent through 30 days following cessation of study treatment must be reported by the investigator.

● All AEs meeting serious criteria, from the time of initial consent through 90 days following cessation of study treatment, or 30 days following cessation of study treatment if the participant initiates new anticancer therapy, whichever is earlier must be reported by the investigator.

● All pregnancies and exposure during breastfeeding, from the time of initial consent through 120 days following cessation of study treatment, or 30 days following cessation of study treatment if the participant initiates new anticancer therapy must be reported by the investigator.

● Additionally, any SAE brought to the attention of an investigator at any time outside of the time period specified above must be reported immediately by the investigator if the event is considered to be drug-related.

Investigators are not obligated to actively seek AE or SAE or other reportable safety events in former study participants. However, if the investigator learns of any SAE, including a death,

at any time after a participant has been discharged from the study, and he/she considers the event to be reasonably related to the study treatment or study participation, the investigator must promptly notify Merck.

7.2.1 Definition of an Overdose for This Protocol and Reporting of Overdose to the UCLA DSMB and to Merck

For purposes of this study, an overdose of pembrolizumab will be defined as any dose of 1,000 mg or greater (≥5 times the indicated dose). No specific information is available on the treatment of overdose of pembrolizumab. In the event of overdose, the participant 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.

If a dose of Merck's product meeting the protocol definition of overdose is taken without any associated clinical symptoms or abnormal laboratory results, the overdose is reported as a non-serious Event of Clinical Interest (ECI), using the terminology "accidental or intentional overdose without adverse effect."

All reports of overdose with and without an adverse event must be reported within 24 hours to the Sponsor and within 2 working days to Merck Global Safety. (Attn: Worldwide Product Safety; FAX 215-661-6229)

7.2.2 Reporting of Pregnancy and Lactation to the UCLA DSMB and to Merck

Although pregnancy and infant exposure during breast feeding are not considered adverse events, it is the responsibility of investigators or their designees to report any pregnancy or lactation in a participant (spontaneously reported to them) that occurs during the study.

Pregnancies and infant exposures during breastfeeding that occur after the consent form is signed but before treatment allocation/randomization must be reported by the investigator if they cause the participant to be excluded from the trial, or are the result of a protocol-specified intervention, including but not limited to washout or discontinuation of usual therapy, diet, placebo treatment or a procedure.

Pregnancies and infant exposures during breastfeeding that occur from the time of treatment allocation/randomization through 120 days following cessation of Sponsor's product, or 30 days following cessation of treatment if the participant initiates new anticancer therapy, whichever is earlier, must be reported by the investigator. All reported pregnancies 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 events (Important Medical 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 the Sponsor and within 2 working days to Merck Global Safety. (Attn: Worldwide Product Safety; FAX 215-661-6229)

7.2.3 Immediate Reporting of Adverse Events to the Sponsor and to Merck

7.2.3.1 Serious Adverse Events

A serious adverse event is any adverse event occurring at any dose or during any use of Merck's product that:

- Results in death;
- Is life threatening;
- Results in persistent or significant disability/incapacity;
- Results in or prolongs an existing inpatient hospitalization;
- Results in a congenital anomaly/birth defect;
- Is an other important medical event.

- **Note:** In addition to the above criteria, adverse events meeting either of the below criteria, although not serious per ICH definition, are reportable to the Merck in the same timeframe as SAEs to meet certain local requirements. Therefore, these events are considered serious by Merck for collection purposes.
- Is a new cancer (that is not a condition of the study);
- Is associated with an overdose.

Refer to Table 7 for additional details regarding each of the above criteria.

For the time period beginning when the consent form is signed until treatment allocation, any serious adverse event, or follow up to a serious adverse event, including death due to any cause that occurs to any participant must be reported within 24 hours to the Sponsor and within 2 working days to Merck Global Safety if it causes the participant to be excluded from the trial, or is the result of a protocol-specified intervention, including but not limited to washout or discontinuation of usual therapy, diet, placebo treatment or a procedure.

For the time period beginning at treatment allocation through 90 days following cessation of treatment, or 30 days following cessation of treatment if the participant initiates new anticancer therapy, whichever is earlier, any serious adverse event, or follow up to a serious adverse event, including death due to any cause whether or not related to the Merck product, must be reported within 24 hours to the Sponsor and within 2 working days to Merck Global Safety.

Additionally, any serious adverse event, considered by an investigator who is a qualified physician to be related to Merck product that is brought to the attention of the investigator at any time following consent through the end of the specified safety follow-up period specified in the paragraph above, or at any time outside of the time period specified in the previous paragraph also must be reported immediately to Merck Global Safety.

All participants with serious adverse events must be followed up for outcome.

SAE reports and any other relevant safety information are to be forwarded to the Merck Global Safety facsimile number: +1-215-661-6229

A copy of all 15 Day Reports and Annual Progress Reports is submitted as required by FDA, European Union (EU), Pharmaceutical and Medical Devices agency (PMDA) or other local regulators. Investigators will cross reference this submission according to local regulations to the Merck Investigational Compound Number (IND, CSA, etc.) at the time of submission. Additionally, investigators will submit a copy of these reports to Merck & Co., Inc. (Attn: Worldwide Product Safety; FAX 215-661-6229) at the time of submission to FDA.

7.2.3.2 Events of Clinical Interest

Selected non-serious and serious adverse events are also known as Events of Clinical Interest (ECI) and must be reported within 2 working days to Merck Global Safety. (Attn: Worldwide Product Safety; FAX 215-661-6229).

For the time period beginning when the consent form is signed until treatment allocation/randomization, any ECI, or follow up to an ECI, that occurs to any participant must be reported within 2 working days to Merck Global Safety if it causes the participant to be excluded from the trial, or is the result of a protocol-specified intervention, including but not limited to washout or discontinuation of usual therapy, diet, placebo treatment or a procedure.

For the time period beginning at treatment allocation/randomization through 90 days following cessation of treatment, or 30 days following cessation of treatment if the participant initiates new anticancer therapy, whichever is earlier, any ECI, or follow up to an ECI, whether or not related to Merck product, must be reported within 2 working days to Merck Global Safety.

Events of clinical interest for this trial include:

1. an overdose of Merck product, as defined in Section 7.2.1 - Definition of an Overdose for This Protocol and Reporting of Overdose to the Sponsor, that is not associated with clinical symptoms or abnormal laboratory results.

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 documents. The purpose of the criteria is to specify a threshold of abnormal hepatic tests that may require an additional evaluation for an underlying etiology.

7.2.4 Evaluating Adverse Events

An investigator who is a qualified physician will evaluate all adverse events according to the NCI Common Terminology for Adverse Events (CTCAE), version 4.0. Any adverse event

which changes CTCAE grade over the course of a given episode will have each change of grade recorded on the adverse event case report forms/worksheets.

All adverse events regardless of CTCAE grade must also be evaluated for seriousness.

Table 7 Evaluating Adverse Events

An investigator who is a qualified physician, will evaluate all adverse events as to:

V4.0 CTCAE Grading	**Grade 1**	**Mild; asymptomatic or mid symptoms; clinical or diagnostic observations only; intervention not indicated.**
	Grade 2	**Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL.**
	Grade 3	**Severe or medically significant but not immediately life-threatening; hospitalization or prolongation or hospitalization indicated; disabling; limiting self-care ADL.**
	Grade 4	**Life threatening consequences; urgent intervention indicated.**
	Grade 5	**Death related to AE**
Seriousness	A serious adverse event is any adverse event occurring at any dose or during any use of Merck product that:	
	†**Results in death**; or	
	†**Is life threatening; or** places the participant, in the view of the investigator, at immediate risk of death from the event as it occurred (Note: This does not include an adverse event that, had it occurred in a more severe form, might have caused death.); or	
	†**Results in a persistent or significant disability/incapacity** (substantial disruption of one's ability to conduct normal life functions); or	
	†**Results in or prolongs an existing inpatient hospitalization** (hospitalization is defined as an inpatient admission, regardless of length of stay, even if the hospitalization is a precautionary measure for continued observation. (Note: Hospitalization for an elective procedure to treat a pre-existing condition that has not worsened is not a serious adverse event. A pre-existing condition is a clinical condition that is diagnosed prior to the use of a Merck product and is documented in the patient's medical history.); or	
	†**Is a congenital anomaly/birth defect** (in offspring of participant taking the product regardless of time to diagnosis);or	
	Is a new **cancer** (that is not a condition of the study) **(**although not serious per ICH definition, is reportable to the Sponsor within 24 hours and to Merck within 2 working days to meet certain local requirements); **or**	
	Is an overdose (whether accidental or intentional). Any adverse event associated with an overdose is considered a serious adverse event for collection purposes. An overdose that is not associated with an adverse event is considered a non-serious event of clinical interest and must be reported within 24 hours to the Sponsor and to Merck within 2 working days..	

	Other important medical events that may not result in death, not be life threatening, or not require hospitalization may be considered a serious adverse event when, based upon appropriate medical judgment, the event may jeopardize the participant and may require medical or surgical intervention to prevent one of the outcomes listed previously (designated above by a †).	
Duration	Record the start and stop dates of the adverse event. If less than 1 day, indicate the appropriate length of time and units	
Action taken	Did the adverse event cause Merck product to be discontinued?	
Relationship to Merck Product	Did Merck product cause the adverse event? The determination of the likelihood that Merck product caused the adverse event will be provided by an investigator who is a qualified physician. The investigator's signed/dated initials on the source document or worksheet that supports the causality noted on the AE form, ensures that a medically qualified assessment of causality was done. This initialed document must be retained for the required regulatory time frame. The criteria below are intended as reference guidelines to assist the investigator in assessing the likelihood of a relationship between the test drug and the adverse event based upon the available information. **The following components are to be used to assess the relationship between Merck product and the AE**; the greater the correlation with the components and their respective elements (in number and/or intensity), the more likely Merck product caused the adverse event (AE):	
	Exposure	Is there evidence that the participant was actually exposed to Merck product such as: reliable history, acceptable compliance assessment (pill count, diary, etc.), expected pharmacologic effect, or measurement of drug/metabolite in bodily specimen?
	Time Course	Did the AE follow in a reasonable temporal sequence from administration of Merck product? Is the time of onset of the AE compatible with a drug-induced effect (applies to trials with investigational medicinal product)?
	Likely Cause	Is the AE not reasonably explained by another etiology such as underlying disease, other drug(s)/vaccine(s), or other host or environmental factors

Relationship to Merck Product (continued)	**The following components are to be used to assess the relationship between the test drug and the AE: (continued)**	
	Dechallenge	Was Merck product discontinued or dose/exposure/frequency reduced? If yes, did the AE resolve or improve? If yes, this is a positive dechallenge. If no, this is a negative dechallenge. (Note: This criterion is not applicable if: (1) the AE resulted in death or permanent disability; (2) the AE resolved/improved despite continuation of the Sponsor's product; or (3) the trial is a single-dose drug trial); or (4) Sponsor's product(s) is/are only used one time.)
	Rechallenge	Was the participant re-exposed to Merck product in this study? If yes, did the AE recur or worsen? If yes, this is a positive rechallenge. If no, this is a negative rechallenge. (Note: This criterion is not applicable if: (1) the initial AE resulted in death or permanent disability, or (2) the trial is a single-dose drug trial); or (3) Sponsor's product(s) is/are used only one time). NOTE: IF A RECHALLENGE IS PLANNED FOR AN ADVERSE EVENT WHICH WAS SERIOUS AND WHICH MAY HAVE BEEN CAUSED BY MERCK PRODUCT, OR IF REEXPOSURE TO MERCK PRODUCT POSES ADDITIONAL POTENTIAL SIGNIFICANT RISK TO THE PARTICIPANT, THEN THE RECHALLENGE MUST BE APPROVED IN ADVANCE BY THE SPONSOR AS PER DOSE MODIFICATION GUIDELINES IN THE PROTOCOL.
	Consistency with Trial Treatment Profile	Is the clinical/pathological presentation of the AE consistent with previous knowledge regarding Merck product or drug class pharmacology or toxicology?
The assessment of relationship will be reported on the case report forms /worksheets by an investigator who is a qualified physician according to his/her best clinical judgment, including consideration of the above elements.		
Record one of the following		**Use the following scale of criteria as guidance (not all criteria must be present to be indicative of Merck product relationship).**
Yes, there is a reasonable possibility of Merck product relationship.		There is evidence of exposure to Merck product. The temporal sequence of the AE onset relative to the administration of Merck product is reasonable. The AE is more likely explained by Merck product than by another cause.
No, there is not a reasonable possibility of Merck product relationship		Participant did not receive the Merck product OR temporal sequence of the AE onset relative to administration of Merck product is not reasonable OR the AE is more likely explained by another cause than the Merck product. (Also entered for a participant with overdose without an associated AE.)

7.2.5 Sponsor Responsibility for Reporting Adverse Events

All Adverse Events will be reported to regulatory authorities, IRB/IECs and investigators in accordance with all applicable global laws and regulations.

7.3 Trial Governance and Oversight

7.3.1 UCLA JCCC Data Safety and Monitoring Board (DSMB) Oversight

This trial will be overseen by the UCLA Jonsson Comprehensive Cancer Center (JCCC) DSMB. The JCCC DSMB meets monthly to review all SAE reports for trials overseen by the JCCC DSMB. All SAE reports, which have been filed since the previous meeting, are presented to the committee for review.

For trials overseen by the JCCC DSMB, the DSMB reviews all dose-limiting toxicities (DLTs) for dose-escalation studies. Protocol suspensions and re-opening of accrual to the next cohort based on DLT evaluation fall under the purview of the DSMB.

For all JCCC oncology trials and TRIO-US studies where the JCCC DSMB has primary oversight, all SAEs shall be reported to the JCCC DSMB in a timely manner [ten days, two days for a death] regardless of relationship and expectedness. The JCCC ORC will review all submissions and the ORC staff will enter the information into the JCCC Clinical Trials database. Reports are generated for full JCCC DSMB review. For trials where the JCCC DSMB has primary DSMB review responsibility, the DSMB requires that the PI generate cumulative adverse event reports for quarterly, biannual or annual review.

The DSMB reviews each SAE report and determines whether or not protocol modifications are warranted to ensure subject safety. In this review, prior occurrences of similar toxicity with the therapy under study are taken into consideration, as well as the severity of the event and the likelihood that it was related to a study drug. The DSMB may recommend no changes to the study if the event is expected or related to other causes such as the subject's underlying condition. The DSMB may request an expert's advice of another non-Principal Investigator with national experience to support their deliberations and decisions.

The JCCC DSMB has the authority to recommend to the UCLA IRB the immediate halt to a study (i.e., discontinuation of any further treatment of enrolled subjects and discontinuation of enrollment of new subjects) should there be any serious unexpected toxicity that warrants further investigation.

Requests for single subject exceptions/waivers from the approved study protocol, including out of window procedures and eligibility deviations, must be reviewed and approved by a member of the DSMB. Each trial is assigned a primary and secondary reviewer who is responsible for reviewing each exception/waiver request for that trial. Approvals and disapprovals of the request are sent to the Principal Investigator via email and copied to the UCLA IRB. Requests for single subject exceptions/waivers are made by the Principal Investigator via email utilizing the "Single Subject Exception Request Form."

JCCC DSMB correspondence are addressed to the Principal Investigator and copied to the UCLA IRB. Minutes of the DSMB meetings are maintained in a computer file.

Confidentiality: Each member of the JCCC DSMB is responsible for maintaining strict confidentiality of the study data. Members will not share any study data or information about the study with any individual external to the JCCC DSMB or the statistical working group for the study. The DSMB members may contact the statistical working group directly with questions regarding the operational details associated with the data analysis and summary presentations. Communication of deliberations or recommendations of the JCCC DSMB, either written or oral, should not be made outside of the Committee or the statistical working group. Outcome results are strictly confidential and must not be divulged to any non-member of the JCCC DSMB except in those cases where DSMB is required to inform the UCLA IRB of its determinations. Disclosure of outcome results to the IRB must only occur with written approval of the DSMB. A member who believes he or she may have a potential intellectual or financial conflict of interest during the course of review of the data must inform the chairperson of the DSMB. In such case, the meeting minutes will record the disclosure of the potential conflict of interest and that the individual recuse himself from the discussions and abstains from voting on the DSMB decision.

7.3.2 Assignment of Risk – Level 2

All interventional clinical trials undergo scientific review by the Internal Scientific Peer Review Committee (ISPRC), which requires that a Data and Safety Monitoring Plan is in place before a trial can be approved to begin. For trials overseen by the JCCC DSMB, the JCCC DSMB will determine the degree of risk of the study and will ensure that there are procedures in place to ensure the safety of the subjects that are enrolled in the trial. The intensity level of study oversight is determined by the risk category. Some of the factors that are considered when assigning the Level of Risk category include:

- A biostatistical design and appropriate procedures for proper data management so that the information collected can be properly validated.
- Appropriate Serious Adverse Event reporting procedures must be in place.
- The study duration must be appropriate and must be based on a realistic rate of enrollment.
- Data collection and data management must be adequate to verify and ensure subject eligibility.

7.3.2.1 Assignment of Risk

This protocol is assigned a Level 2 Risk. Assigning risk ensures that the data and safety monitoring is based on the level of risk (low, medium, or high) to ensure that the data and safety monitoring activities are appropriate. Level 2 Risk assignment includes the data and safety monitoring activities listed below:

- Compliance Officer meets with PI/Staff prior to study initiation; review regulatory requirements and operating system. Compliance Officer provides real time monitoring to determine eligibility prior to enrollment onto the protocol.
- Real time QA monitoring of the subjects and data collection occurs for all subjects entered onto the trial.
- Comprehensive QA auditing within first year or first 10 subjects enrolled, whichever comes first. Subsequent audit frequency will be annually.
- Frequency of DSMB Summary Report is typically on a biannual basis or approximately every six months.

7.3.3 Monitoring and Auditing Activities

The compliance officer of the JCCC Office of Regulatory Compliance [ORC] will monitor and audit the clinical records for all human subjects enrolled onto JCCC trials overseen by the JCCC DSMB. The JCCC compliance officer will perform real time review of informed consent processes and the meeting of all inclusion and exclusion criteria and screening results at study entry. Active monitoring will offer the JCCC study teams prospective information that can be used to enhance the quality of research being performed contemporaneously. Auditing is a review of historic performance of the research effort and is performed on case report forms, regulatory files and source documents to measure the quality of the research effort in a retrospective manner.

8.0 STATISTICAL ANALYSIS PLAN SUMMARY

8.1 Statistical Analysis Plan

This section outlines the statistical analysis plan for the study. This is a non-randomized, multi-center, multi-cohort, open-label, Phase Ib trial of pembrolizumab (MK-3475) in combination with platinum-based chemotherapy with Cohort 1) naïve small cell cancer of the bladder, urethra, or upper urinary tract, and with Cohort 2) primary small cell or neuroendocrine prostate cancer.

8.1.1 Efficacy Analysis Plan

In both cohorts, all assessments will be based on investigator assessments of tumor response, recurrence, progression, and cause of death. The efficacy endpoints for this study are as follows:

- DRR will be defined as the durable response rate (PFS at 6 month).

- ORR based on RECIST 1.1 criteria (Cohort 1 and 2) and biochemical PSA response (Cohort 2). ORR will be determined as the proportion of subjects who have a CR or PR by RECIST 1.1. PSA response will be defined as a PSA decline of ≥50% from baseline measured twice at least 3 weeks apart.

- DOR based on RECIST 1.1 criteria (Cohort 1 and 2) and biochemical PSA response (Cohort 2). DOR will be defined as the time from the first documented CR or PR until radiograph disease progression by RECIST 1.1 or PSA progression. PSA progression will be defined as the date that an increase of 25% or more and an absolute increase of ≥2 ng/ml above nadir occurs.

- PFS based on RECIST 1.1 criteria (Cohort 1 and 2) and biochemical PSA response (Cohort 2). PFS will be defined as the time from the first day of study treatment to first documented disease progression or PSA progression as defined above.

- rPFS based on PCWG3 criteria (Cohort 2). rPFS will be defined as the time from the first day of study treatment to first documented disease progression as defined above.

- OS is defined as the time from the first day of study treatment to the time of death from any cause. Patients who have not died will be censored at the last date known to be alive.

There is no formal hypothesis testing for the trial. All statistical analyses will be performed after the study is completed and the database is locked and released. Statistical analyses will be performed using SAS software or other validated statistical software as required.

The statistical analyses will be primarily descriptive and exploratory. The proportional data (DRR, ORR) will be summarized using 95% 2-sided exact Binomial CIs. Time-to-event data (DOR, PFS and OS) will be summarized by cohort using the Kaplan-Meier method. Kaplan-Meier estimates of event rates at landmark time points (e.g., 3-,6-, and 12-months) and median time to the event will be presented with the corresponding 95% CIs.

8.1.2 Safety Analysis Plan

The secondary objective for this study is to determine safety and tolerability of pembrolizumab in combination with etoposide and cisplatin/carboplatin or docetaxel and carboplatin chemotherapy. Safety will be assessed through summaries of adverse events, changes in laboratory test results, and changes in selected vital signs. Safety analysis will be based on subjects who experienced toxicities as defined by CTCAE Version 4.0 criteria. Safety will be assessed by quantifying the toxicities and grades experienced by subjects who have received pembrolizumab. The attribution to drug, time-of-onset, duration of the event, its resolution, and any concomitant medications administered will be recorded. Adverse events will be analyzed including but not limited to all AEs, SAEs, fatal AEs, and clinically significant laboratory changes.

The mandatory Safety Follow-up Visit will be conducted approximately 30 days after the last dose of trial treatment or before the initiation of a new anti-neoplastic treatment, whichever comes first. All AEs that occur prior to the Safety Follow-up Visit should be recorded. Subjects with an AE of Grade >1 will be followed until the resolution of the AE to Grade 0-1 or until the beginning of a new anti- neoplastic therapy, whichever occurs first. Serious adverse events will be collected for 90 days after the trial treatment or 30 days after the end of treatment if the subject initiates new anti-cancer therapy, whichever is earlier.

8.1.3 Exploratory Endpoints

Potential correlations of PD-L1 expression, serum, circulating cell, urine, and tissue molecular molecular (genomic, metabolic, proteomic) biomarkers with the safety and clinical response of pembrolizumab combined with platinum-based chemotherapy will be explored.

8.2 Sample Size Consideration

This study is not designed to make explicit power and Type I error considerations for hypothesis testing. Instead, this study is designed to obtain preliminary efficacy as measured by DRR, ORR, DOR, PFS, and OS and determine safety and tolerability of pembrolizumab in combination with platinum-based chemotherapy.

The primary endpoint of the efficacy analyses will be DRR. Only descriptive statistical analysis will be performed for this signal finding study. Sample size calculation was not based on statistical hypothesis testing.

9.0 LABELING, PACKAGING, STORAGE AND RETURN OF CLINICAL SUPPLIES

9.1 Investigational Product

The 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.

Pembrolizumab will be provided by Merck as summarized in Table 8.

Table 8 Product Descriptions

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

9.2 Packaging and Labeling Information

Supplies will be labeled in accordance with regulatory requirements.

9.3 Clinical Supplies Disclosure

This trial is open-label; therefore, the participant, the trial site personnel, the Sponsor and/or designee are not blinded to treatment. Drug identity (name, strength) is included in the label text; random code/disclosure envelopes or lists are not provided.

9.4 Storage and Handling Requirements

Clinical supplies must be stored in a secure, limited-access location under the storage conditions specified on the label.

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

Clinical supplies may not be used for any purpose other than that stated in the protocol.

9.5 Returns and Reconciliation

The investigator is responsible for keeping accurate records of the clinical supplies received from Merck or designee, the amount dispensed to and returned by the participants and the amount remaining at the conclusion of the trial.

Upon completion or termination of the study, all unused and/or partially used investigational product will be destroyed at the site per institutional policy. It is the Investigator's responsibility to arrange for disposal of all empty containers, provided that procedures for proper disposal have been established according to applicable federal, state, local and institutional guidelines and procedures, and provided that appropriate records of disposal are kept.

10.0 REFERENCES

1. Scher, H. I.; Morris, M. J.; Stadler, W. M.; Higano, C. S.; Halabi, S.; Smith, M. R.; Basch, E. M.; Fizazi, K.; Ryan, C. J.; Antonarakis, E. S.; Corn, P. G.; Liu, G.; Bono, J. S. De; Schwartz, L. H.; Beer, T. M.; Kelly, W. K.; Hussain, M.; Sartor, A. O.; Kantoff, P. W.; Armstrong, A. J. The Prostate Cancer Working Group 3 (PCWG3) Consensus for Trials in Castration-Resistant Prostate Cancer (CRPC). *Journal of Clinical Oncology* **2015**, *33*.

2. Disis, M. L. Immune Regulation of Cancer. *J. Clin. Oncol.* **2010**, *28*, 4531–4538.

3. Dudley, M. E.; Wunderlich, J. R.; Yang, J. C.; Sherry, R. M.; Topalian, S. L.; Restifo,

N. P.; Royal, R. E.; Kammula, U.; White, D. E.; Mavroukakis, S. A.; Rogers, L. J.; Gracia, G. J.; Jones, S. A.; Mangiameli, D. P.; Pelletier, M. M.; Gea-Banacloche, J.; Robinson, M. R.; Berman, D. M.; Filie, A. C.; Abati, A.; Rosenberg, S. A. Adoptive Cell Transfer Therapy Following Non-Myeloablative but Lymphodepleting Chemotherapy for the Treatment of Patients with Refractory Metastatic Melanoma. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology* **2005**, *23*, 2346–57.

4. Hunder, N. N.; Wallen, H.; Cao, J.; Hendricks, D. W.; Reilly, J. Z.; Rodmyre, R.; Jungbluth, A.; Gnjatic, S.; Thompson, J. A.; Yee, C. Treatment of Metastatic Melanoma with Autologous CD4+ T Cells against NY-ESO-1. *The New England journal of medicine* **2008**, *358*, 2698–703.

5. Greenwald, R. J.; Freeman, G. J.; Sharpe, A. H. THE B7 FAMILY REVISITED. *Annual Review of Immunology* **2005**, *23*, 515–548.

6. Okazaki, T.; Maeda, A.; Nishimura, H.; Kurosaki, T.; Honjo, T. PD-1 Immunoreceptor Inhibits B Cell Receptor-Mediated Signaling by Recruiting Src Homology 2-Domain-Containing Tyrosine Phosphatase 2 to Phosphotyrosine. *Proceedings of the National Academy of Sciences of the United States of America* **2001**, *98*, 13866–71.

7. Zhang, X.; Schwartz, J. C. D.; Guo, X.; Bhatia, S.; Cao, E.; Chen, L.; Zhang, Z. Y.; Edidin, M. A.; Nathenson, S. G.; Almo, S. C. Structural and Functional Analysis of the Costimulatory Receptor Programmed Death-1. *Immunity* **2004**, *20*, 337–347.

8. Chemnitz, J. M.; Parry, R. V.; Nichols, K. E.; June, C. H.; Riley, J. L. SHP-1 and SHP-2 Associate with Immunoreceptor Tyrosine-Based Switch Motif of Programmed Death 1 upon Primary Human T Cell Stimulation, but Only Receptor Ligation Prevents T Cell Activation. *The Journal of Immunology* **2004**, *173*, 945–954.

9. Sheppard, K. A.; Fitz, L. J.; Lee, J. M.; Benander, C.; George, J. A.; Wooters, J.; Qiu, Y.; Jussif, J. M.; Carter, L. L.; Wood, C. R.; Chaudhary, D. PD-1 Inhibits T-Cell Receptor Induced Phosphorylation of the ZAP70/CD3?? Signalosome and Downstream Signaling to PKC?? *FEBS Letters* **2004**, *574*, 37–41.

10. Riley, J. L. PD-1 Signaling in Primary T Cells. *Immunol. Rev.* **2009**, *229*, 114–125.

11. Parry, R. V.; Chemnitz, J. M.; Frauwirth, K. A.; Lanfranco, A. R.; Braunstein, I.; Kobayashi, S. V.; Linsley, P. S.; Thompson, C. B.; Riley, J. L. CTLA-4 and PD-1 Receptors Inhibit T-Cell Activation by Distinct Mechanisms. *Molecular and Cellular Biology* **2005**, *25*, 9543–9553.

12. Francisco, L. M.; Sage, P. T.; Sharpe, A. H. The PD-1 Pathway in Tolerance and Autoimmunity. *Immunol. Rev.* **2010**, *236*, 219–242.

13. Ott, P. A.; Bang, Y. J.; Berton-Rigaud, D.; Elez, E.; Pishvaian, M. J.; Rugo, H. S.; Puzanov, I.; Mehnert, J. M.; Aung, K. L.; Lopez, J.; Carrigan, M.; Saraf, S.; Chen, M.;

Soria, J. C. Safety and Antitumor Activity of Pembrolizumab in Advanced Programmed Death Ligand 1–Positive Endometrial Cancer: Results from the KEYNOTE-028 Study. *Journal of Clinical Oncology* **2017**, *35*, 2535–2541.

14. Langer, C. J.; Gadgeel, S. M.; Borghaei, H.; Papadimitrakopoulou, V. A.; Patnaik, A.; Powell, S. F.; Gentzler, R. D.; Martins, R. G.; Stevenson, J. P.; Jalal, S. I.; Panwalkar, A.; Yang, J. C. H.; Gubens, M.; Sequist, L. V.; Awad, M. M.; Fiore, J.; Ge, Y.; Raftopoulos, H.; Gandhi, L. Carboplatin and Pemetrexed with or without Pembrolizumab for Advanced, Non-Squamous Non-Small-Cell Lung Cancer: A Randomised, Phase 2 Cohort of the Open-Label KEYNOTE-021 Study. *The Lancet Oncology* **2016**, *17*, 1497–1508.

15. Lara, P.; Beckett, L.; Li, Y.; Parikh, M.; Robles, D.; Aujla, P. Combination Checkpoint Immunotherapy and Cytotoxic Chemotherapy: Pembrolizumab plus Either Docetaxel or Gemcitabine in Patients with Advanced or Metastatic Urothelial Cancer. *J Clin Oncol* **2017**, *35*, 398.

16. Merchan, J. R.; Jhaveri, K. D. Chemotherapy Nephrotoxicity and Dose Modification in Patients with Kidney Impairment: Conventional Cytotoxic Agents. *Up To Date*.

17. Tannock, I. F.; Wit, R. de; Berry, W. R.; Horti, J.; Pluzanska, A.; Chi, K. N.; Oudard, S.; Théodore, C.; James, N. D.; Turesson, I.; Rosenthal, M. A.; Eisenberger, M. A. Docetaxel plus Prednisone or Mitoxantrone plus Prednisone for Advanced Prostate Cancer. *New England Journal of Medicine* **2004**, *351*, 1502–1512.

18. Moretto, P.; Wood, L.; Emmenegger, U.; Blais, N.; Mukherjee, S. D.; Winquist, E.; Belanger, E. C.; MacRae, R.; Balogh, A.; Cagiannos, I.; Kassouf, W.; Black, P.; Czaykowski, P.; Gingerich, J.; North, S.; Ernst, S.; Richter, S.; Sridhar, S.; Reaume, M. N.; Soulieres, D.; Eisen, A.; Canil, C. M. Management of Small Cell Carcinoma of the Bladder: Consensus Guidelines from the Canadian Association of Genitourinary Medical Oncologists (CAGMO). *Journal of the Canadian Urological Association* **2013**, *7*.

19. Anker, C. J.; Dechet, C.; Isaac, J. C.; Akerley, W.; Shrieve, D. C. Small-Cell Carcinoma of the Prostate. *Journal of Clinical Oncology* **2008**, *26*, 1168–1171.

20. Galsky, M. D.; Hahn, N. M.; Rosenberg, J.; Sonpavde, G.; Hutson, T.; Oh, W. K.; Dreicer, R.; Vogelzang, N.; Sternberg, C. N.; Bajorin, D. F.; Bellmunt, J. Treatment of Patients with Metastatic Urothelial Cancer "Unfit" for Cisplatin-Based Chemotherapy. *J. Clin. Oncol.* **2011**, *29*, 2432–2438.

21. Roth, B. J.; Johnson, D. H.; Einhorn, L. H.; Schacter, L. P.; Cherng, N. C.; Cohen, H. J.; Crawford, J.; Randolph, J. A.; Goodlow, J. L.; Broun, G. O.; Omura, G. A.; Greco, F. A. Randomized Study of Cyclophosphamide, Doxorubicin, and Vincristine versus Etoposide and Cisplatin versus Alternation of These Two Regimens in Extensive Small-Cell Lung Cancer: A Phase III Trial of the Southeastern Cancer Study Group. *Journal*

of Clinical Oncology **1992**, *10*, 282–291.

22. Sundstrøm, S.; Bremnes, R. M.; Kaasa, S.; Aasebø, U.; Hatlevoll, R.; Dahle, R.; Boye, N.; Wang, M.; Vigander, T.; Vilsvik, J.; Skovlund, E.; Hannisdal, E.; Aamdal, S.; Norwegian Lung Cancer Study Group Cisplatin and Etoposide Regimen Is Superior to Cyclophosphamide, Epirubicin, and Vincristine Regimen in Small-Cell Lung Cancer: Results from a Randomized Phase III Trial with 5 Years' Follow-Up. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology* **2002**, *20*, 4665–72.

23. Lynch, S. P.; Shen, Y.; Kamat, A.; Grossman, H. B.; Shah, J. B.; Millikan, R. E.; Dinney, C. P.; Siefker-Radtke, A. Neoadjuvant Chemotherapy in Small Cell Urothelial Cancer Improves Pathologic Downstaging and Long-Term Outcomes: Results from a Retrospective Study at the Md Anderson Cancer Center. *European Urology* **2013**, *64*, 307–313.

24. QUEK, M.; NICHOLS, P.; YAMZON, J.; DANESHMAND, S.; MIRANDA, G.; CAI, J.; GROSHEN, S.; STEIN, J.; SKINNER, D. RADICAL CYSTECTOMY FOR PRIMARY NEUROENDOCRINE TUMORS OF THE BLADDER: THE UNIVERSITY OF SOUTHERN CALIFORNIA EXPERIENCE. *The Journal of Urology* **2005**, *174*, 93–96.

25. SIEFKER-RADTKE, A. O.; DINNEY, C. P.; ABRAHAMS, N. A.; MORAN, C.; SHEN, Y. U.; PISTERS, L. L.; GROSSMAN, H. B.; SWANSON, D. A.; MILLIKAN, R. E. EVIDENCE SUPPORTING PREOPERATIVE CHEMOTHERAPY FOR SMALL CELL CARCINOMA OF THE BLADDER: A RETROSPECTIVE REVIEW OF THE M. D. ANDERSON CANCER EXPERIENCE. *The Journal of Urology* **2004**, *172*, 481–484.

26. Bex, A.; Nieuwenhuijzen, J. A.; Kerst, M.; Pos, F.; Boven, H. Van; Meinhardt, W.; Horenblas, S. Small Cell Carcinoma of Bladder: A Single-Center Prospective Study of 25 Cases Treated in Analogy to Small Cell Lung Cancer. *Urology* **2005**, *65*, 295–299.

27. Ismaili, N.; Heudel, P. E.; Elkarak, F.; Kaikani, W.; Bajard, A.; Ismaili, M.; Errihani, H.; Droz, J. P.; Flechon, A. Outcome of Recurrent and Metastatic Small Cell Carcinoma of the Bladder. *BMC Urology* **2009**, *9*, 4.

28. Loehrer, P. J.; Einhorn, L. H.; Elson, P. J.; Crawford, E. D.; Kuebler, P.; Tannock, I.; Raghavan, D.; Stuart-Harris, R.; Sarosdy, M. F.; Lowe, B. A.; Blumenstein, B.; Trump, D. A Randomized Comparison of Cisplatin Alone or in Combination with Methotrexate, Vinblastine, and Doxorubicin in Patients with Metastatic Urothelial Carcinoma: A Cooperative Group Study. *Journal of Clinical Oncology* **1992**, *10*, 1066–1073.

29. Saxman, S. B.; Propert, K. J.; Einhorn, L. H.; Crawford, E. D.; Tannock, I.; Raghavan, D.; Loehrer, P. J.; Trump, D. Long-Term Follow-up of a Phase III Intergroup Study of Cisplatin Alone or in Combination with Methotrexate, Vinblastine, and Doxorubicin in

Patients with Metastatic Urothelial Carcinoma: A Cooperative Group Study. *Journal of Clinical Oncology* **1997**, *15*, 2564–2569.

30. Maase, H. von der; Hansen, S. W.; Roberts, J. T.; Dogliotti, L.; Oliver, T.; Moore, M. J.; Bodrogi, I.; Albers, P.; Knuth, A.; Lippert, C. M.; Kerbrat, P.; Sanchez Rovira, P.; Wersall, P.; Cleall, S. P.; Roychowdhury, D. F.; Tomlin, I.; Visseren-Grul, C. M.; Conte, P. F. Gemcitabine and Cisplatin versus Methotrexate, Vinblastine, Doxorubicin, and Cisplatin in Advanced or Metastatic Bladder Cancer: Results of a Large, Randomized, Multinational, Multicenter, Phase III Study. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology* **2000**, *18*, 3068–77.

31. Galsky, M. D.; Chen, G. J.; Oh, W. K.; Bellmunt, J.; Roth, B. J.; Petrioli, R.; Dogliotti, L.; Dreicer, R.; Sonpavde, G. Comparative Effectiveness of Cisplatin-Based and Carboplatin-Based Chemotherapy for Treatment of Advanced Urothelial Carcinoma. *Annals of oncology : official journal of the European Society for Medical Oncology / ESMO* **2012**, *23*, 406–10.

32. Siefker-Radtke, A. O.; Kamat, A. M.; Grossman, H. B.; Williams, D. L.; Qiao, W.; Thall, P. F.; Dinney, C. P.; Millikan, R. E. Phase II Clinical Trial of Neoadjuvant Alternating Doublet Chemotherapy with Ifosfamide/Doxorubicin and Etoposide/Cisplatin in Small-Cell Urothelial Cancer. *Journal of Clinical Oncology* **2009**, *27*, 2592–2597.

33. Amato, R. J.; Logothetis, C. J.; Hallinan, R.; Ro, J. Y.; Sella, A.; Dexeus, F. H. Chemotherapy for Small Cell Carcinoma of Prostatic Origin. *The Journal of Urology* **1992**, *147*, 935–937.

34. Vlachostergios, P. J.; Papandreou, C. N. Targeting Neuroendocrine Prostate Cancer: Molecular and Clinical Perspectives. *Frontiers in Oncology* **2015**, *5*.

35. Aparicio, A. M.; Harzstark, A. L.; Corn, P. G.; Wen, S.; Araujo, J. C.; Tu, S. M.; Pagliaro, L. C.; Kim, J.; Millikan, R. E.; Ryan, C.; Tannir, N. M.; Zurita, A. J.; Mathew, P.; Arap, W.; Troncoso, P.; Thall, P. F.; Logothetis, C. J. Platinum-Based Chemotherapy for Variant Castrate-Resistant Prostate Cancer. *Clinical Cancer Research* **2013**, *19*, 3621–3630.

36. Brennan, S. M.; Gregory, D. L.; Stillie, A.; Herschtal, A.; Manus, M. Mac; Ball, D. L. Should Extrapulmonary Small Cell Cancer Be Managed like Small Cell Lung Cancer? *Cancer* **2010**, *116*, 888–895.

37. Chen, Z.; Fillmore, C. M.; Hammerman, P. S.; Kim, C. F.; Wong, K.-K. Non-Small-Cell Lung Cancers: A Heterogeneous Set of Diseases. *Nature Reviews Cancer* **2015**, *15*, 247–247.

38. Walenkamp, A. M. E.; Sonke, G. S.; Sleijfer, D. T. Clinical and Therapeutic Aspects of Extrapulmonary Small Cell Carcinoma. *Cancer treatment reviews* **2009**, *35*, 228–36.

39. Antoni, S.; Ferlay, J.; Soerjomataram, I.; Znaor, A.; Jemal, A.; Bray, F. Bladder Cancer Incidence and Mortality: A Global Overview and Recent Trends. *European Urology* **2016**, *71*, 96–108.

40. Thota, S.; Kistangari, G.; Daw, H.; Spiro, T. A Clinical Review of Small-Cell Carcinoma of the Urinary Bladder. *Clin. Genitourin. Cancer* **2013**, *11*, 73–77.

41. Ghervan, L.; Zaharie, A.; Ene, B.; Elec, F. I. Small-Cell Carcinoma of the Urinary Bladder: Where Do We Stand? *Clujul Medical* **2017**, *90*.

42. Lerner, S. P. et al No Title. *J Clin Oncol* **2017**, *35*, Abstr 4500.

43. Sjödahl, G.; Eriksson, P.; Liedberg, F.; Höglund, M. Molecular Classification of Urothelial Carcinoma: Global MRNA Classification versus Tumour-Cell Phenotype Classification. *Journal of Pathology* **2017**, *242*, 113–125.

44. Fitzmaurice, C.; Allen, C.; Barber, R. M.; Barregard, L.; Bhutta, Z. A.; Brenner, H.; Dicker, D. J.; Chimed-Orchir, O.; Dandona, R.; Dandona, L.; Fleming, T.; Forouzanfar, M. H.; Hancock, J.; Hay, R. J.; Hunter-Merrill, R.; Huynh, C.; Hosgood, H. D.; Johnson, C. O.; Jonas, J. B.; Khubchandani, J.; Kumar, G. A.; Kutz, M.; Lan, Q.; Larson, H. J.; Liang, X.; Lim, S. S.; Lopez, A. D.; MacIntyre, M. F.; Marczak, L.; Marquez, N.; Mokdad, A. H.; Pinho, C.; Pourmalek, F.; Salomon, J. A.; Sanabria, J. R.; Sandar, L.; Sartorius, B.; Schwartz, S. M.; Shackelford, K. A.; Shibuya, K.; Stanaway, J.; Steiner, C.; Sun, J.; Takahashi, K.; Vollset, S. E.; Vos, T.; Wagner, J. A.; Wang, H.; Westerman, R.; Zeeb, H.; Zoeckler, L.; Abd-Allah, F.; Ahmed, M. B.; Alabed, S.; Alam, N. K.; Aldhahri, S. F.; Alem, G.; Alemayohu, M. A.; Ali, R.; Al-Raddadi, R.; Amare, A.; Amoako, Y.; Artaman, A.; Asayesh, H.; Atnafu, N.; Awasthi, A.; Saleem, H. B.; Barac, A.; Bedi, N.; Bensenor, I.; Berhane, A.; Bernabé, E.; Betsu, B.; Binagwaho, A.; Boneya, D.; Campos-Nonato, I.; Castañeda-Orjuela, C.; Catalá-López, F.; Chiang, P.; Chibueze, C.; Chitheer, A.; Choi, J.-Y.; Cowie, B.; Damtew, S.; Neves, J. das; Dey, S.; Dharmaratne, S.; Dhillon, P.; Ding, E.; Driscoll, T.; Ekwueme, D.; Endries, A. Y.; Farvid, M.; Farzadfar, F.; Fernandes, J.; Fischer, F.; G/hiwot, T. T.; Gebru, A.; Gopalani, S.; Hailu, A.; et al. Global, Regional, and National Cancer Incidence, Mortality, Years of Life Lost, Years Lived With Disability, and Disability-Adjusted Life-Years for 32 Cancer Groups, 1990 to 2015. *JAMA Oncology* **2017**, *3*, 524.

45. Small, E. J. et al. No Title. *J Clin Oncol* **2015**, *33*.

46. Siegel, R. L.; Miller, K. D.; Jemal, A. Cancer Statistics, 2017. *CA: A Cancer Journal for Clinicians* **2017**, *67*, 7–30.

47. Lee, J. K.; Phillips, J. W.; Smith, B. A.; Park, J. W.; Stoyanova, T.; McCaffrey, E. F.; Baertsch, R.; Sokolov, A.; Meyerowitz, J. G.; Mathis, C.; Cheng, D.; Stuart, J. M.; Shokat, K. M.; Gustafson, W. C.; Huang, J.; Witte, O. N. N-Myc Drives Neuroendocrine Prostate Cancer Initiated from Human Prostate Epithelial Cells. *Cancer Cell* **2016**, *29*, 536–547.

48. Ishii, H.; Azuma, K.; Kawahara, A.; Yamada, K.; Imamura, Y.; Tokito, T.; Kinoshita, T.; Kage, M.; Hoshino, T. Significance of Programmed Cell Death-Ligand 1 Expression and Its Association with Survival in Patients with Small Cell Lung Cancer. *Journal of thoracic oncology : official publication of the International Association for the Study of Lung Cancer* **2015**, *10*, 426–30.

49. George, J.; Saito, M.; Tsuta, K.; Iwakawa, R.; Shiraishi, K.; Scheel, A. H.; Uchida, S.; Watanabe, S. I.; Nishikawa, R.; Noguchi, M.; Peifer, M.; Jang, S. J.; Petersen, I.; Buttner, R.; Harris, C. C.; Yokota, J.; Thomas, R. K.; Kohno, T. Genomic Amplification of CD274 (PD-L1) in Small-Cell Lung Cancer. *Clinical Cancer Research* **2017**, *23*, 1220–1226.

50. Wilde, L.; Ali, S. M.; Solomides, C. C.; Ross, J. S.; Trabulsi, E.; Hoffman-Censits, J. Response to Pembrolizumab in a Patient With Chemotherapy Refractory Bladder Cancer With Small Cell Variant Histology: A Case Report and Review of the Literature. *Clinical Genitourinary Cancer* **2017**, *15*, e521–e524.

51. Cheun, H.; Kim, M.; Lee, H.; Oh, K. H.; Keam, B. Safety and Efficacy of Immune Checkpoint Inhibitors for End-Stage Renal Disease Patients Undergoing Dialysis: A Retrospective Case Series and Literature Review. *Investigational New Drugs* **2019**.

52. Park, S.; Daniels, G. A. Anti-PD-1 Therapy in Patients with End-Stage Renal Disease on Dialysis: A Single-Center Case Series. *Journal of Clinical Oncology* **2017**.

53. Kanz, B. A.; Pollack, M. H.; Johnpulle, R.; Puzanov, I.; Horn, L.; Morgans, A.; Sosman, J. A.; Rapisuwon, S.; Conry, R. M.; Eroglu, Z.; Johnson, D. B. Safety and Efficacy of Anti-PD-1 in Patients with Baseline Cardiac, Renal, or Hepatic Dysfunction. *Journal for ImmunoTherapy of Cancer* **2016**.

54. Hirsch, J. S.; Wanchoo, R.; Ng, J. H.; Khanin, Y.; Jhaveri, K. D. Use of Immune Checkpoint Inhibitors in End Stage Kidney Disease Patients, Single Center Experience and Review of the Literature. *Kidney360* **2020**, *1*, 399–402.

55. Seymour, L.; Bogaerts, J.; Perrone, A.; Ford, R.; Schwartz, L. H.; Mandrekar, S.; Lin, N. U.; Litière, S.; Dancey, J.; Chen, A.; Hodi, F. S.; Therasse, P.; Hoekstra, O. S.; Shankar, L. K.; Wolchok, J. D.; Ballinger, M.; Caramella, C.; Vries, E. G. E. de IRECIST: Guidelines for Response Criteria for Use in Trials Testing Immunotherapeutics. *Lancet Oncol.* **2017**, *18*, e143–e152.

56. Collisson, E. A.; Campbell, J. D.; Brooks, A. N.; Berger, A. H.; Lee, W.; Chmielecki, J.; Beer, D. G.; Cope, L.; Creighton, C. J.; Danilova, L.; Ding, L.; Getz, G.; Hammerman, P. S.; Neil Hayes, D.; Hernandez, B.; Herman, J. G.; Heymach, J. V.; Jurisica, I.; Kucherlapati, R.; Kwiatkowski, D.; Ladanyi, M.; Robertson, G.; Schultz, N.; Shen, R.; Sinha, R.; Sougnez, C.; Tsao, M.-S.; Travis, W. D.; Weinstein, J. N.; Wigle, D. A.; Wilkerson, M. D.; Chu, A.; Cherniack, A. D.; Hadjipanayis, A.; Rosenberg, M.; Weisenberger, D. J.; Laird, P. W.; Radenbaugh, A.; Ma, S.; Stuart, J.

M.; Averett Byers, L.; Baylin, S. B.; Govindan, R.; Meyerson, M.; Rosenberg, M.; Gabriel, S. B.; Cibulskis, K.; Sougnez, C.; Kim, J.; Stewart, C.; Lichtenstein, L.; Lander, E. S.; Lawrence, M. S.; Getz, G.; Kandoth, C.; Fulton, R.; Fulton, L. L.; McLellan, M. D.; Wilson, R. K.; Ye, K.; Fronick, C. C.; Maher, C. A.; Miller, C. A.; Wendl, M. C.; Cabanski, C.; Ding, L.; Mardis, E.; Govindan, R.; Creighton, C. J.; Wheeler, D.; Balasundaram, M.; Butterfield, Y. S. N.; Carlsen, R.; Chu, A.; Chuah, E.; Dhalla, N.; Guin, R.; Hirst, C.; Lee, D.; Li, H. I.; Mayo, M.; Moore, R. A.; Mungall, A. J.; Schein, J. E.; Sipahimalani, P.; Tam, A.; Varhol, R.; Gordon Robertson, A.; Wye, N.; Thiessen, N.; Holt, R. A.; Jones, S. J. M.; Marra, M. A.; Campbell, J. D.; Brooks, A. N.; Chmielecki, J.; Imielinski, M.; Onofrio, R. C.; Hodis, E.; Zack, T.; et al. Comprehensive Molecular Profiling of Lung Adenocarcinoma. *Nature* **2014**, *511*, 543–550.

57. George, J.; Lim, J. S.; Jang, S. J.; Cun, Y.; Ozretić, L.; Kong, G.; Leenders, F.; Lu, X.; Fernández-Cuesta, L.; Bosco, G.; Müller, C.; Dahmen, I.; Jahchan, N. S.; Park, K.-S.; Yang, D.; Karnezis, A. N.; Vaka, D.; Torres, A.; Wang, M. S.; Korbel, J. O.; Menon, R.; Chun, S.-M.; Kim, D.; Wilkerson, M.; Hayes, N.; Engelmann, D.; Pützer, B.; Bos, M.; Michels, S.; Vlasic, I.; Seidel, D.; Pinther, B.; Schaub, P.; Becker, C.; Altmüller, J.; Yokota, J.; Kohno, T.; Iwakawa, R.; Tsuta, K.; Noguchi, M.; Muley, T.; Hoffmann, H.; Schnabel, P. A.; Petersen, I.; Chen, Y.; Soltermann, A.; Tischler, V.; Choi, C.; Kim, Y.-H.; Massion, P. P.; Zou, Y.; Jovanovic, D.; Kontic, M.; Wright, G. M.; Russell, P. A.; Solomon, B.; Koch, I.; Lindner, M.; Muscarella, L. A.; Torre, A. la; Field, J. K.; Jakopovic, M.; Knezevic, J.; Castaños-Vélez, E.; Roz, L.; Pastorino, U.; Brustugun, O.-T.; Lund-Iversen, M.; Thunnissen, E.; Köhler, J.; Schuler, M.; Botling, J.; Sandelin, M.; Sanchez-Cespedes, M.; Salvesen, H. B.; Achter, V.; Lang, U.; Bogus, M.; Schneider, P. M.; Zander, T.; Ansén, S.; Hallek, M.; Wolf, J.; Vingron, M.; Yatabe, Y.; Travis, W. D.; Nürnberg, P.; Reinhardt, C.; Perner, S.; Heukamp, L.; Büttner, R.; Haas, S. A.; Brambilla, E.; Peifer, M.; Sage, J.; Thomas, R. K. Comprehensive Genomic Profiles of Small Cell Lung Cancer. *Nature* **2015**, *524*, 47–53.

58. Beltran, H.; Prandi, D.; Mosquera, J. M.; Benelli, M.; Puca, L.; Cyrta, J.; Marotz, C.; Giannopoulou, E.; Chakravarthi, B. V. S. K.; Varambally, S.; Tomlins, S. A.; Nanus, D. M.; Tagawa, S. T.; Allen, E. M. Van; Elemento, O.; Sboner, A.; Garraway, L. A.; Rubin, M. A.; Demichelis, F. Divergent Clonal Evolution of Castration-Resistant Neuroendocrine Prostate Cancer. *Nature Medicine* **2016**, *22*, 298–305.

59. Plaisier, S. B.; Taschereau, R.; Wong, J. A.; Graeber, T. G. Rank-Rank Hypergeometric Overlap: Identification of Statistically Significant Overlap between Gene-Expression Signatures. *Nucleic acids research* **2010**, *38*, e169.

11.0 APPENDICES

Appendix 1: ECOG Performance Status

Grade	Description
0	Normal activity. Fully active, able to carry on all pre-disease performance without restriction.
1	Symptoms, but ambulatory. Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature (e.g., light housework, office work).
2	In bed <50% of the time. Ambulatory and capable of all self-care, but unable to carry out any work activities. Up and about more than 50% of waking hours.
3	In bed >50% of the time. Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.
4	100% bedridden. Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.
5	Dead.

* As published in Am. J. Clin. Oncol.: *Oken, M.M., Creech, R.H., Tormey, D.C., Horton, J., Davis, T.E., McFadden, E.T., Carbone, P.P.: Toxicity And Response Criteria Of The Eastern Cooperative Oncology Group. Am J Clin Oncol 5:649-655, 1982.* The Eastern Cooperative Oncology Group, Robert Comis M.D., Group Chair.

Appendix 2: Common Terminology Criteria for Adverse Events V4.0 (CTCAE)

The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 will be utilized for adverse event reporting. (http://ctep.cancer.gov/reporting/ctc.html)

Appendix 3: Contraceptive Guidance and Pregnancy Testing

Woman of Childbearing Potential (WOCBP)

A woman is considered fertile following menarche and until becoming post-menopausal unless permanently sterile (see below)

Women in the following categories are not considered WOCBP:

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

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

- Postmenopausal female
    - A postmenopausal state is defined as no menses for 12 months without an alternative medical cause.
        - A high follicle stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormonal replacement therapy (HRT). However, in the absence of 12 months of amenorrhea, confirmation with two FSH measurements in the postmenopausal range is required.
    - Females on HRT and whose menopausal status is in doubt will be required to use one of the non-hormonal highly effective contraception methods if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of postmenopausal status before study enrollment.

Contraception Requirements

Male Participants:

Male participants with female partners of childbearing potential are eligible to participate if they agree to one of the following during the protocol defined time frame in section 5.1.1:

- Be abstinent from penile-vaginal intercourse as their usual and preferred lifestyle (abstinent on a long term and persistent basis) and agree to remain abstinent

- Use a male condom plus partner use of a contraceptive method with a failure rate of <1% per year as described in Table 9 when having penile-vaginal intercourse with a woman of childbearing potential who is not currently pregnant.

    - Note: Men with a pregnant or breastfeeding partner must agree to remain abstinent from penile-vaginal intercourse or use a male condom during each episode of penile penetration.

Female Participants:

Female participants of childbearing potential are eligible to participate if they agree to use a highly effective method of contraception that has a low user dependency consistently and correctly as described in Table 10 during the protocol-defined time frame in Section 5.1.1.

Table 10 Highly Effective Contraceptive Methods That Have Low User Dependency

Highly Effective Methods That Have Low User Dependency *Failure rate of <1% per year when used consistently and correctly.*
• Progestogen- only contraceptive implant [a, b] • Intrauterine hormone-releasing system (IUS) [b] • Intrauterine device (IUD) • Bilateral tubal occlusion
• **Vasectomized partner** A vasectomized partner is a highly effective contraception method provided that the partner is the sole male sexual partner of the WOCBP and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used.
• **Sexual abstinence** Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study treatment. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant.
Notes: Use should be consistent with local regulations regarding the use of contraceptive methods for participants of clinical studies. a) If locally required, in accordance with Clinical Trial Facilitation Group (CTFG) guidelines, acceptable contraceptive implants are limited to those which inhibit ovulation. b) If hormonal contraception efficacy is potentially decreased due to interaction with study treatment, condoms must be used in addition to the hormonal contraception during the treatment period and for at least [X days, corresponding to time needed to eliminate study treatment plus 30 days for study treatments with genotoxic potential] after the last dose of study treatment.

Pregnancy Testing

WOCBP should only be included after a negative highly sensitive urine or serum pregnancy test and in accordance with local requirements. When applicable this test should be repeated a maximum of 24-hours before the first dose/vaccination.

Following initiation of treatment additional pregnancy testing will be performed at monthly intervals during the treatment period and at 30 days after the last dose of study treatment and as required locally.

Pregnancy testing will be performed whenever an expected menstrual cycle is missed or when pregnancy is otherwise suspected.

Appendix 4: Description of the iRECIST Process for Assessment of Disease Progression

Assessment at Screening and Prior to RECIST 1.1 Progression

Until radiographic progression based on RECIST 1.1, there is no distinct iRECIST assessment.

Assessment and Decision at RECIST 1.1 Progression

In participants who show evidence of radiological PD by RECIST 1.1 the Investigator will decide whether to continue a participant on study treatment until repeat imaging is obtained (using iRECIST for participant management (see Table 5 and Figures 1 and 3). This decision by the Investigator should be based on the participant's overall clinical condition.

Clinical stability is defined as the following:

- Absence of symptoms and signs indicating clinically significant progression of disease
- No decline in ECOG performance status
- No requirements for intensified management, including increased analgesia, radiation, or other palliative care

Any participant deemed clinically unstable should be discontinued from study treatment at site-assessed first radiologic evidence of PD, and is not required to have repeat tumor imaging for confirmation of PD by iRECIST.

If the Investigator decides to continue treatment, the participant may continue to receive study treatment and the tumor assessment should be repeated 4 to 8 weeks later to confirm PD by iRECIST, per Investigator assessment. I

Tumor flare may manifest as any factor causing radiographic progression per RECIST 1.1, including:

- Increase in the sum of diameters of target lesion(s) identified at baseline to ≥ 20% and ≥ 5 mm from nadir
    - Please note: the iRECIST publication uses the terminology "sum of measurements", but "sum of diameters" will be used in this protocol, consistent with the original RECIST 1.1 terminology.
- Unequivocal progression of non-target lesion(s) identified at baseline
- Development of new lesion(s)

iRECIST defines new response categories, including iUPD (unconfirmed progressive disease) and iCPD (confirmed progressive disease). For purposes of iRECIST assessment, the first visit showing progression according to RECIST 1.1 will be assigned a visit (overall) response of iUPD, regardless of which factors caused the progression.

At this visit, target and non-target lesions identified at baseline by RECIST 1.1 will be assessed as usual.

New lesions will be classified as measurable or non-measurable, using the same size thresholds and rules as for baseline lesion assessment in RECIST 1.1. From measurable new lesions, up to 5 lesions total (up to 2 per organ), may be selected as New Lesions – Target. The sum of diameters of these lesions will be calculated, and kept distinct from the sum of diameters for target lesions at baseline. All other new lesions will be followed qualitatively as New Lesions – Non-target.

Assessment at the Confirmatory Imaging

On the confirmatory imaging, the participant will be classified as progression confirmed (with an overall response of iCPD), or as showing persistent unconfirmed progression (with an overall response of iUPD), or as showing disease stability or response (iSD/iPR/iCR).

Confirmation of Progression

Progression is considered confirmed, and the overall response will be iCPD, if ANY of the following occurs:

- Any of the factors that were the basis for the initial iUPD show worsening
    - For target lesions, worsening is a further increase in the sum of diameters of ≥ 5 mm, compared to any prior iUPD time point
    - For non-target lesions, worsening is any significant growth in lesions overall, compared to a prior iUPD time point; this does not have to meet the "unequivocal" standard of RECIST 1.1
    - For new lesions, worsening is any of these:
        - An increase in the new lesion sum of diameters by ≥ 5 mm from a prior iUPD time point
        - Visible growth of new non-target lesions
        - The appearance of additional new lesions
- Any new factor appears that would have triggered PD by RECIST 1.1

Persistent iUPD

Progression is considered not confirmed, and the overall response remains iUPD, if:

- None of the progression-confirming factors identified above occurs AND
- The target lesion sum of diameters (initial target lesions) remains above the initial PD threshold (by RECIST 1.1)

Additional imaging for confirmation should be scheduled 4 to 8 weeks from the scan on which iUPD is seen. This may correspond to the next visit in the original visit schedule. The assessment of the subsequent confirmation scan proceeds in an identical manner, with possible outcomes of iCPD, iUPD, and iSD/iPR/iCR.

Resolution of iUPD

Progression is considered not confirmed, and the overall response becomes iSD/iPR/iCR, if:

- None of the progression-confirming factors identified above occurs, AND
- The target lesion sum of diameters (initial target lesions) is not above the initial PD threshold.

The response is classified as iSD or iPR (depending on the sum of diameters of the target lesions), or iCR if all lesions resolve.

In this case, the initial iUPD is considered to be pseudo-progression, and the level of suspicion for progression is "reset". This means that the next visit that shows radiographic progression, whenever it occurs, is again classified as iUPD by iRECIST, and the confirmation process is repeated before a response of iCPD can be assigned.

Management Following the Confirmatory Imaging

If repeat imaging does not confirm PD per iRECIST, as assessed by the Investigator, and the participant continues to be clinically stable, study treatment may continue and follow the regular imaging schedule. If PD is confirmed, participants will be discontinued from study treatment.

NOTE: If a participant has confirmed radiographic progression (iCPD) as defined above, but the participant is achieving a clinically meaningful benefit, an exception to continue study treatment may be considered. In this case, if study treatment is continued, tumor imaging should continue to be performed following the intervals as outlined in Section 6.

Detection of Progression at Visits After Pseudo-progression Resolves

After resolution of pseudo-progression (ie, achievement of iSD/iPR/iCR), iUPD is indicated by any of the following events:

- Target lesions
    - Sum of diameters reaches the PD threshold ($\geq 20\%$ and ≥ 5 mm increase from nadir) either for the first time, or after resolution of previous pseudo-progression. The nadir is always the smallest sum of diameters seen during the entire trial, either before or after an instance of pseudo-progression.
- Non-target lesions

- If non-target lesions have never shown unequivocal progression, their doing so for the first time results in iUPD.
- If non-target lesions had shown previous unequivocal progression, and this progression has not resolved, iUPD results from any significant further growth of non-target lesions, taken as a whole.

- New lesions
  - New lesions appear for the first time
  - Additional new lesions appear
  - Previously identified new target lesions show an increase of ≥ 5 mm in the new lesion sum of diameters, from the nadir value of that sum
  - Previously identified non-target lesions show any significant growth

If any of the events above occur, the overall response for that visit is iUPD, and the iUPD evaluation process (see Assessment at the Confirmatory Imaging above) is repeated. Progression must be confirmed before iCPD can occur.

The decision process is identical to the iUPD confirmation process for the initial PD, except in one respect. If new lesions occurred at a prior instance of iUPD, and at the confirmatory scan the burden of new lesions has increased from its smallest value (for new target lesions, their sum of diameters is ≥5 mm increased from its nadir), then iUPD cannot resolve to iSD or iPR. It will remain iUPD until either a decrease in the new lesion burden allows resolution to iSD or iPR, or until a confirmatory factor causes iCPD.

Additional details about iRECIST are provided in the iRECIST publication [55].