Cover Page for Protocol

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PD-L1 Inhibition as ChecKpoint Immunotherapy for NeuroEndocrine Phenotype Prostate Cancer (PICK NEPC)

DUKE CANCER INSTITUTE

A National Cancer Institute-designated Comprehensive Cancer Center

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External Sites Participating in This Study

TBD

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1 PROTOCOL SYNOPSIS

Study Title: PD-L1 Inhibition as CheckPoint Immunotherapy for NeuroEndocrine Phenotype Prostate Cancer (PICK NEPC)					
Protocol Number	Pro00080869	**Phase**	II	**Type**	Interventional
Condition/Disease: Neuroendocrine prostate cancer (NEPC)					
Number of Subjects	18 in stage 1, 49 overall	**Duration of Subject Participation**			3 years
Number of Study Centers	3-4	**Duration of Study** 8 years			Anticipated 12-18 months accrual time per stage, up to 3 years follow up

Rationale:

Neuroendocrine Prostate Cancer

Using the SEER database, there are an estimated 180,890 new cases of prostate cancer in the United Stated in 2016 with an associated 26,120 deaths for that year.[1] Of those cases, most have adenocarcinoma histology with an estimated 586.0 cases per million per year, but there are multiple other non-adenocarcinoma histologies as well.[2] Although a much less common form of prostate cancer, men with neuroendocrine differentiation of their prostate cancer have a much worse prognosis with median overall survival (OS) of 7 months (mo) compared with years in men with adenocarcinoma.[3] Much of the poor survival related to these patients is related to the fact that all the currently approved therapies for metastatic castration resistant prostate cancer (mCRPC) including docetaxel,[4] cabazitaxel,[5] abiraterone,[6,7] enzalutamide,[8,9] radium-223,[10] Sipuleucel-T[11] are only proven and effective in patients with adenocarcinoma. Therefore to date there are no phase 3 studies that definitively show an overall survival benefit in men with neuroendocrine differentiation which highlights the need for more effective therapies in these men.

Neuroendocrine prostate cancer (NEPC) lies on a spectrum of aggressive prostate cancer along with small cell prostate cancer (SCPC) and was defined originally by histology that was similar to neuroendocrine tumors of other origins.[12] SCPC has classic histologic features such as small tumor cells with scanty cytoplasm, darkly stained nuclei with homogeneous chromatin pattern and do not form glandular structures but grow as solid sheets with frequent mitotic figures and necrosis. Different from SCPC, NEPC has been harder to classify as a group and is now being redefined to be intermediate atypical carcinoma (IAC) of the prostate with histologic features distinct from small cell carcinoma or adenocarcinoma.[13] IAC grows as solid sheets or vague glandular structures, has moderate amounts of cytoplasm and centrally located, round and regular nuclei with fine, granular and homogeneous chromatin. Mitosis and necrosis are absent. NEPC spectra histologies have a very aggressive clinical phenotype and often have low PSA (as these tumors do not make it), predominant visceral spread, osteolytic and not osteoblastic bone lesions, bulky lymphadenopathy, and the development of castration resistance within 6 months of androgen deprivation therapy (ADT).[14] In addition, NEPC tumors have a higher mutational burden than typical adenocarcinoma suggesting an opportunity for immunotherapy in this disease.[15]

NEPC can not only be present from the onset of diagnosis but also transform out of treated mCRPC and is likely found in 20-30% of castration-resistant tumors compared to 5-10% at initial diagnosis.[12] Since this treatment-related NEPC is becoming more recognized and common and since it is very resistant to the conventional therapies of mCRPC, new therapies need to be developed for men with this disease.

Treatments for NEPC and Study Rationale

Currently the standard of care for treating NEPC and its spectrum of diseases is to start with ADT as most NEPCs are mixed with adenocarcinoma. Once the cancer has become CRPC or if the histology at diagnosis was small cell

prostate cancer (SCPC), the therapy tends to focus on using platinum combination therapy. Although there are no phase 3 trials looking at these therapies the literature shows that many patients have been treated with cisplatin and etoposide.[14,16-18] Although platinums appear to have a benefit in NEPC, none of them have been curative or led to long term remission in the vast majority of men. In mCRPC platinums have been tested alone or in combination with other chemotherapies and the results have shown some dramatic successes with soft tissue response rates in the 70s and 80s in some studies while other have been in the teens.[19] Platinums act through DNA damage and it is conjectured that patients with inherited DNA-repair gene mutation, which is approximately 12% of metastatic prostate cancer,[20] or acquired DNA-repair gene mutations may benefit from them as shown in the TOPARP trial,[21] a single arm phase II trial that showed that patients with mCRPC that had DNA-repair defects had better survival and response rates to olaparib a poly(adenosine diphosphate [ADP]-ribose) polymerase inhibitor.

Immune checkpoint blockade is a novel systemic approach in which the patient's own immune system is stimulated to better recognize and destroy cancer cells. Ipilimumab and nivolumab, blocking monoclonal antibodies to CTLA-4 and programed-death receptor-1 (PD-1) respectively, acts to over stimulate the immune system and both have been studied in melanoma both as single agents and in combination to improve the overall survival of patients with melanoma.[22,23]

Although the small cell histology is rare in prostate cancer, it is common in lung cancer. Small cell lung cancer (SCLC) like that of the prostate has a poor overall survival. Currently the mainstay of chemotherapy in SCLC is combination cisplatin with etoposide which is where SCPC got the direction to be treated by these agents given the similarity of histology. Recently a phase 1/2 trial was performed that enrolled patients with progressive lung SCLC to nivolumab with and without ipilimumab in varying dose combinations.[24] The results demonstrated that the nivolumab alone arm had 15% with partial response and 22.5% with stable disease compared to 5% (1 patient) with a complete response, 20% with partial response, and 30% with stable disease in the combination arm. Not only were there responses in each arm, some appeared to be durable. These data suggest efficacy of PD-1 inhibition in patients with neuroendocrine lung cancers.

Avelumab

Avelumab is a fully human antibody that specifically targets and blocks PD-L1, thus removing the suppressive effects of PD-L1 on the anti-tumor CD8+ T cells. It has been studies in Phase I and II trials including patients with non-small cell lung cancer, ovarian cancer, and Merkel cell carcinoma. The NSCLC expansion cohort had an objective response rate (ORR) of 14.1% (26 of 184 NSCLC subjects).[25] An ovarian cancer expansion cohort had an ORR of 10.7% (8 of 75 subjects).[26] The Phase II trial in Merkel Cell carcinoma gave avelumab to 88 patients and resulted in an objective response in 31.8%, including 8 complete responses.[27]

Data supporting PD-L1 inhibition in prostate cancer was found when enzalutamide resistant cell lines and xenografts on mice had increased PD-L1.[28] Our own cell lines established at Duke that are enzalutamide resistant also demonstrate upregulation of PD-L1 at the protein and RNA level as compared with the parental cell lines, suggesting that PD-L1 is an adaptive response to stress and is highly dynamic (data unpublished). Further, we have also looked at a cohort of patients with NEPC/SCPC using a tissue microarray for PD-L1 expression by immunohistochemistry and have found that a small subset (~20% small cell, ~10% adenocarcinoma) of these cases express high levels of PD-L1 (data unpublished). Further still is evidence showing that there is a high burden of genetic mutations in NEPC[29] which has been seen in other cancers to confer susceptibility to immunotherapy.

Given the emerging role of immunotherapy across multiple tumor types to produce durable responses, and given the similarity of small cell by both histology and its response to current chemotherapy, we hypothesize that avelumab will produce a clinical and radiographic response in NEPC that will be durable in a subset of patients. In this study, we are defining the NEPC "phenotype" based on clinical poor risk features of AR-independence or based on histologic evidence of NEPC in tissue or serum.

Primary Objective: To determine the efficacy of PD-L1 inhibition with avelumab as measured by a modified PCWG3,[30] where RECIST 1.1[31] is replaced with iRECIST, a modified RECIST 1.1 for immune-based therapeutics,[32] radiographic response rate in men with metastatic neuroendocrine-like prostate cancer.

Secondary Objectives:

1. To describe the efficacy of PD-L1 inhibition with avelumab as measured by PCWG3 using RECIST1.1
2. To describe the radiographic progression free survival (rPFS) of PD-L1 inhibition with avelumab using modified PCWG3 with both RECIST 1.1 and iRECIST criteria in this setting.
3. To describe the overall survival of PD-L1 inhibition in this setting.
4. To described the toxicities and safety of PD-L1 inhibition with avelumab in men with metastatic neuroendocrine-like prostate cancer.

Exploratory Objectives:

1. To describe the impact of PD-L1 inhibition with avelumab on blood-based biomarker changes over time, including PSA, chromogranin-A, cell free DNA, LDH, and alkaline phosphatase.
2. To determine if levels of circulating biomarkers secreted by neuroendocrine-like prostate cancers correlate with clinical and radiographic treatment response
3. To determine if the presence of different immunohistochemical markers on the pre-biopsy specimens prognosticates clinical and radiographic treatment response
4. To determine if the level of different circulating immune cells correlate with both progressive addition of immunotherapy as well as clinical and radiographic treatment response or disease progression
5. To determine if levels of cell free DNA correlate with clinical and radiographic treatment response
6. To isolate prostate neuroendocrine-like CTCs for ex vivo growth and culture and characterization studies.

Hypothesis:

We hypothesize that PD-L1 inhibition with avelumab will be efficacious based on radiographic responses in a subset of men with metastatic neuroendocrine-like prostate cancer and be reasonably well tolerated, meeting criteria for further study in larger phase 2 and 3 trials based on meeting pre-specified efficacy rates and prolonged PFS in some men.

Design:

This is a phase 2, open-label, single arm trial of avelumab in men with metastatic neuroendocrine-like prostate cancer. Men who meet inclusion criteria (without exclusions) will be started on avelumab 10 mg/kg IV every 2 weeks and will stay on therapy until progression or intolerable side effects. Cycles will be 4 weeks long and thus include 2 doses of avelumab. Baseline tissue will be assessed histologically for eligibility at Duke and for correlative tissue biomarkers. Treatment beyond radiologic or PSA progression is permitted after approval of the PI of the study and if the providing physician and patient determine that there is potential for clinical benefit with continued therapy.

At radiologic progression a standard of care post-treatment progression biopsy will be collected at the discretion of the treating provider, and if proper consent is obtained, additional tissue will be collected for research tests including assessments of resistance mechanisms and immune checkpoint status. The additional research tissue will be banked in the Biospecimen Repository & Processing Core (BRPC) under Pro00080869. The study team will also pursue dual consent to BRPC Pro00035974 for future unspecified research.

Men will continue on their ADT used at entry into study per investigator with subsequent changes made per investigator. Men not on ADT at time of entry due to being purely SCPC may remain off ADT. Men with SCPC on ADT at study entry should remain on ADT per investigator while all men with mixed histologies should remain on active ADT during trial participation.

Men will be allowed to receive palliative radiation to any disease site indicated by the treating physician at any time during the study, provided that another untreated site of measureable disease is present at baseline. All subjects will be followed for disease progression and mortality for up to 3 years from the date that the subjects were enrolled to the protocol.

Study Population: This is a non-blinded single arm-arm phase II study of approximately 49 subjects, to assess the safety and efficacy of avelumab in patients with mCRPC. Eligible men will have metastatic CRPC with NEPC phenotype with measureable disease at baseline.

The target sample size is 18 in stage 1, and overall 49 evaluable subjects. For stage 1, Duke will serve as the single site for this study. For stage 2, the study would be expanded to include additional sites through the Department of Defense Prostate Cancer Clinical Trials Consortium (DOD PCCTC). All subjects will be followed for disease progression and death from the date that the subjects were enrolled to the protocol.

Selection of Subjects:

Inclusion Criteria:

1. Neuroendocrine-like prostate cancer, based on histology OR based on clinical presentation as defined by meeting one of the two below criteria. All subjects must submit their primary tumor or metastatic biopsy pathology specimens to the Duke Cancer Institute where they will be centrally reviewed by Duke Pathology (Dr. Jiaoti Huang). Central Duke pathologic review is not required for screening but rather for confirmation of histologic subtype. Local pathologic review is sufficient for eligibility determination.
    a. **Criterion 1:** Presence of 1 of 3 histologically proven diagnoses: **1)** Primary small cell carcinoma of the prostate, defined by classic histologic features such as small tumor cells with scanty cytoplasm, darkly stained nuclei with homogeneous chromatin pattern. The tumor cells do not form glandular structure but grow as solid sheets with frequent mitotic figures and necrosis; **2)** Intermediate atypical carcinoma of the prostate, which has histologic features distinct from small cell carcinoma or adenocarcinoma. The tumor grows as solid sheets or vague glandular structures. The tumor cells have moderate amounts of cytoplasm and centrally located, round and regular nuclei with fine, granular and homogeneous chromatin. Mitosis and necrosis are absent; **3)** mixed histology tumors of the prostate, containing both adenocarcinoma and neuroendocrine or small cell components.

b. **Criterion 2:** Presence of histologically proven adenocarcinoma of the prostate without any sign of neuroendocrine or small cell histology that is radiographically progressing despite castrate levels of testosterone (<50 ng/mL) with the following poor risk features:
    i. Prior progression despite therapy with either abiraterone acetate and/or enzalutamide
    ii. At least one of the following: 1) Liver metastases; 2) Bulky radiographic progression (≥2 cm short axis lymph nodes or ≥1 cm long axis visceral metastases) combined with low serum PSA (<10ng/mL); 3) High serum LDH (>1X upper limit of normal).

2. Measurable disease as defined by modified PCWG3 using iRECIST criteria
3. Available tumor tissue for pathologic review and correlative studies. Tumor tissue (localized or metastatic) does not need to be received but rather identified and available (slides and/or blocks) to be sent to Duke.
4. Documented progressive metastatic CRPC based on at least one of the following criteria:
    a. PSA progression defined as 25% increase over baseline value with an increase in the absolute value of at least 2.0 ng/mL that is confirmed by another PSA level with a minimum of a 1 week interval and a minimum PSA of 2.0 ng/mL. Note: If confirmed rise is the only indication of progression, a minimal starting value of 1.0 ng/mL is acceptable, unless pure small-cell carcinoma.
    b. Soft-tissue progression based on new lesions or growth of existing soft tissue metastases.
    c. Progression of bone disease (evaluable disease) or (new bone lesion(s)) by bone scan.

5. Castrate levels of serum total testosterone (≤50 ng/dl) OR ongoing documented ADT unless pure small cell prostate cancer is present.
6. Previous use of radiation to metastatic site(s) at any time prior to enrollment is allowed, provided that this site is not the only measurable disease present or unless that solitary site is progressing following radiation.
7. Patients should have received at least one line of approved chemotherapy and/or hormonal therapy
8. Previous cytotoxic chemotherapy including cisplatin, carboplatin, oxaliplatin, etoposide, docetaxel, cabazitaxel, and gemcitabine is allowed, up to 3 prior regimens.
9. Karnofsky performance status of 70 or higher.
10. Acceptable initial laboratory values within 14 days of Cycle 1 Day 1 according to the below table:

ANC	≥ 1500/µl
Hemoglobin	≥ 9.0 g/dL (prior transfusion is permitted)
Platelet count	≥ 100,000/µl
Creatinine	≤ 2.0 x the institutional upper limit of normal (ULN) OR creatinine clearance >30 ml/min
Potassium	≥ 3.5 mmol/L (within institutional normal range)
Bilirubin	≤ 1.5 x ULN (unless documented Gilbert's disease)
SGOT (AST)	≤ 2.5x ULN, or ≤5x ULN in patients with documented liver metastases
SGPT (ALT)	≤ 2.5x ULN or ≤5x ULN in patients with documented liver metastases

11. Age ≥18
12. Highly effective contraception for male subjects with childbearing potential throughout the study and for at least 60 days after last avelumab treatment administration if the risk of conception exists.
13. Willing and able to provide written informed consent and HIPAA authorization for the release of personal health information.
14. Life expectancy of over 3 months as determined by treating physician.

Exclusion Criteria:

1. Prior usage of PD-1 inhibitors, programed-death ligand 1 and/or 2 inhibitors, CTLA-4 inhibitors including but not limited to ipilimumab, nivolumab, avelumab, durvalumab, tremelimumab, and pembrolizumab.

2. Active on-going immunologic or autoimmune disease including but not limited to systemic or cutaneous lupus erythematosus, cutaneous psoriasis, psoriatic arthritis, rheumatoid arthritis, scleroderma, sicca syndrome, polymyalgia rheumatica, polyarteritis nodosa, granulomatous polyangiitis, microscopic polyangiitis, polyarteritis nodosa, temporal arteritis, giant cell arteritis, dermatomyositis, Kawasaki disease.
3. Previous malignancy within 3 years other than non-melanomatous skin cancers or cancers of low malignant potential such as non-invasive urothelial carcinoma.
4. Any other on-going chemotherapeutic, biologic, radiopharmaceutical, or investigational agent currently or within 28 days of cycle 1 day 1.
5. Prior use of abiraterone and other hormonal agents used to treat prostate cancer are permitted but abiraterone acetate should be stopped prior to study treatment initiation.
6. Current usage of immunosuppressant medication except for a) intranasal, inhaled, and topical corticosteroids and b) systemic corticosteroids equivalent to ≤ 10 mg/day of prednisone, c) steroids as premedication for hypersensitivity reactions (e.g. CT scan premedication).
7. Prior organ transplantation including allogeneic stem-cell transplants.
8. Active bacterial or viral infections requiring systemic therapy.
9. Current active infections with HIV/AIDS, Hepatitis B, and Hepatitis C requiring treatment.
10. Live virus vaccination within 4 weeks of the first dose of avelumab (inactivated vaccines are allowed).
11. Known prior hypersensitivity to the investigational product or any component formulations, including known severe hypersensitivity reactions to monoclonal antibodies.
12. Clinically significant (i.e. active) cardiovascular disease: cerebral vascular accident (<6 months prior to enrollment), myocardial infarction (<6 months prior to enrollment), unstable angina, congestive heart failure (≥ New York Heart Association Classification Class II), or serious cardiac arrhythmia requiring medication.
13. Persisting toxicity related to prior therapy (NCI CTCAE v. 4.03 Grade > 1); however, alopecia, sensory neuropathy Grade ≤ 2, Grade 2 anemia, or other Grade ≤ 2 not constituting a safety risk based on investigator's judgment are acceptable.
14. Other severe acute or chronic medical conditions including colitis, inflammatory bowel disease, pneumonitis, pulmonary fibrosis or psychiatric conditions including recent (within the past year) or active suicidal ideation or behavior; or laboratory abnormalities that may increase the risk associated with study participation or study treatment administration or may interfere with the interpretation of study results and, in the judgment of the investigator, would make the patient inappropriate for entry into this study.

Study Intervention and Administration:

The study agent avelumab will be administered at a dose of 10 mg/kg by IV every 2 weeks until progression or intolerable side effects. Cycles will be 4 weeks long and thus include 2 doses of avelumab. In order to mitigate infusion related reactions, a premedication with an antihistamine and with paracetamol (acetaminophen) 30 to 60 minutes prior to each dose of avelumab is mandatory. Avelumab should be administered in a setting that allows for immediate access to an intensive care unit or equivalent environment and administration of therapy for anaphylaxis, such as the ability to implement immediate resuscitation measures. Avelumab should be given over 2 hours (-10 min/+20min). Steroids (dexamethasone 10 mg), epinephrine (1:1,000 dilution), allergy medications (IV antihistamines), bronchodilators, or equivalents, and oxygen should be available for immediate access. Following avelumab infusions, subjects must be observed for 30 minutes post infusion for potential infusion related reactions. Avelumab will be provided by Pfizer and distributed by DCI Investigational Chemotherapy Service.

Study Assessments:

Vital signs, performance status, physical exam, adverse events and concomitant medications will be assessed at each visit. The following laboratory studies will be obtained at intervals specified in the study flow chart to assess subject safety: complete blood count, serum chemistries, TSH and free T4. Testosterone, blood-based biomarkers (such as PSA, CEA, chromogranin A, etc), immune cells, and cell free DNA will also be assessed for disease status and correlative science. A bone scan and either CT or MRI scans of the chest, abdomen, and pelvis will be performed to assess disease status at baseline as well as every 8 weeks or at treatment discontinuation. Patient reported outcomes will be collected using the Functional Assessment of Cancer Therapy – Prostate (FACT-P) at baseline and

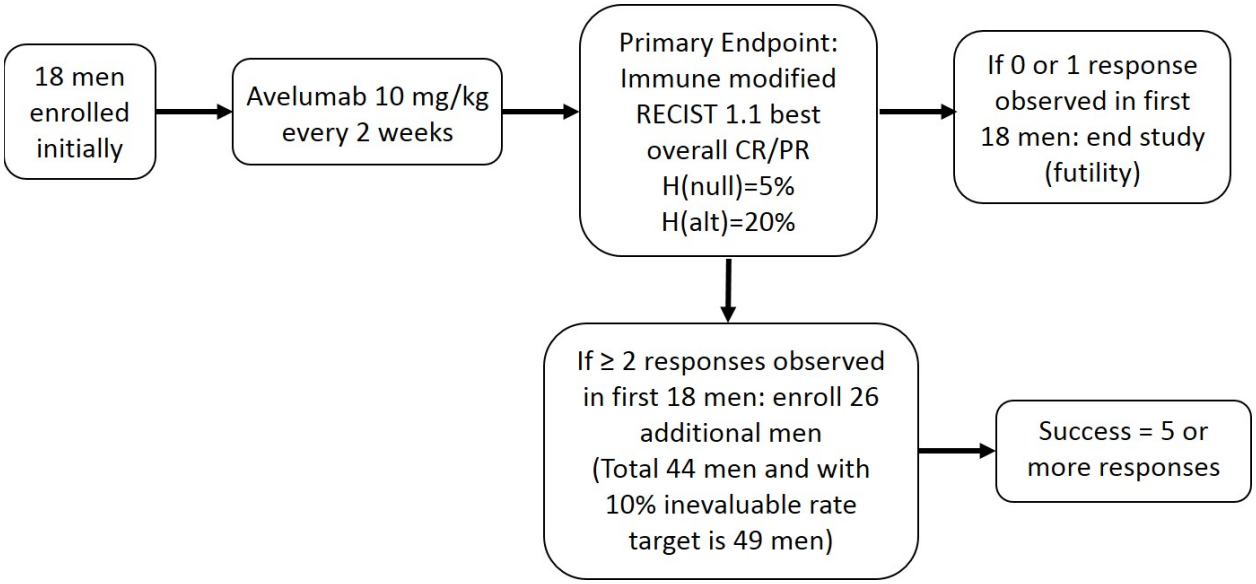
every 3 cycles to assess quality of life. The pre-biopsy specimen obtained during screening and the optional post-progression biopsy will be assessed for correlative biomarkers and resistance mechanisms.

Data Analysis and Statistical Considerations:

This study will use the optimal two-stage Simon design to test the hypothesis about modified PCWG3 using iRECIST radiologic response rate in subjects with NEPC treated with avelumab. Response will be defined as a complete (CR) or partial response (PR) using iRECIST criteria. Assuming that the response rate among subjects treated is 5%, the trial is designed to have 88% power with a one-sided type I error rate=5% to reject the null hypothesis of response rate of 5% when the true response rate was 20%. In the first stage, 18 subjects will be enrolled and if one or fewer responses are observed the trial will be terminated. However, if two or more responses are observed, an additional 26 subjects will be enrolled at the second stage for a total of 44 subjects. If five or more subjects respond, this new agent would be declared to have promising activity. This design has 88% power to conclude an agent is promising if its true objective response proportion is 20%; Type 1 error rate (one-sided) is 0.05 (this is the probability to conclude that a given agent is promising if its true objective response proportion is 5%).The probability of early termination under the null hypothesis is 0.77. These operating characteristics were selected to represent a reasonable compromise between high power, low false positive rates, and desire for small sample sizes, especially in the first stage. Allowing for 10% unevaluable rate, the target sample size is 49 subjects.

With 44 subjects, the objective response rate will be estimated with a standard error no greater than 10.7 percentage points. The Kaplan-Meier method will be used to estimate progression-free survival and overall survival distributions. Summary statistic will be computed for the duration of time on treatment distribution. The correlative science analyses will be considered exploratory and interpreted as such.

2 STUDY SCHEMA



3 BACKGROUND AND SIGNIFICANCE

3.1 Study Disease: Neuroendocrine-like Prostate Cancer

Using the SEER database, there are an estimated 180,890 new cases of prostate cancer in the United Stated in 2016 with an associated 26,120 deaths for that year.[1] Of those cases, most have adenocarcinoma histology with an estimated 586.0 cases per million per year, but there are multiple other non-adenocarcinoma histologies as well.[2] Although a much less common form of prostate cancer, men with neuroendocrine differentiation of their prostate cancer have a much worse prognosis with median overall survival (OS) of 7 months (mo) compared with years in men with adenocarcinoma.[3] Much of the poor survival related to these patients is related to the fact that all the currently approved therapies for metastatic castration resistant prostate cancer (mCRPC) including docetaxel,[4] cabazitaxel,[5] abiraterone,[6,7] enzalutamide,[8,9] radium-223,[10] Sipuleucel-T[11] are only proven and effective in patients with adenocarcinoma. Therefore to date there are no phase 3 studies that definitively show an overall survival benefit in men with neuroendocrine differentiation which highlights the need for more effective therapies in these men.

One difficulty in studying prostate cancer with neuroendocrine differentiation is that diagnostically these cancers are very heterogeneous. Originally neuroendocrine prostate cancer (NEPC) was defined by histology that was similar to neuroendocrine tumors of other origins and includes the subtypes of small-cell, large-cell, and carcinoid.[12] SCPC has classic histologic features such as small tumor cells with scanty cytoplasm, darkly stained nuclei with homogeneous chromatin pattern and do not form glandular structures but grow as solid sheets with frequent mitotic figures and necrosis. Different from SCPC, NEPC has been harder to classify as a group and is now being redefined to be intermediate atypical carcinoma (IAC) of the prostate with histologic features distinct from small cell carcinoma or adenocarcinoma.[13] IAC grows as solid sheets or vague glandular structures, has moderate amounts of cytoplasm and centrally located, round and regular nuclei with fine, granular and homogeneous chromatin. Mitosis and necrosis are absent. The new definition of IAC is also

complimented by having a unique 50 gene signature with 97% accuracy.[13] But in addition to histology, these men with NEPC had a very aggressive clinical phenotype and often had low PSA (as these tumors do not make it), predominant visceral spread, osteolytic and not osteoblastic bone lesions, bulky lymphadenopathy, and the development of castration resistance within 6 months of androgen deprivation therapy (ADT).[14] In addition, NEPC tumors have a higher mutational burden than typical adenocarcinoma suggesting an opportunity for immunotherapy in this disease.[15] Circulating tumor cells from NEPC patients have been studied and shown to have low or absent AR expression, lower cytokeratin expression, and smaller morphology relative to typical CRPC.[33] This disease has also been referred to as aggressive variant prostate cancer or anaplastic prostate cancer, reflecting that some of these tumors with de-differentiation lack neuroendocrine biomarkers but still remain AR independent.

In addition to the difficult classification of the NEPC phenotype, NEPC can not only be present from the onset of diagnosis but also transform out of treated mCRPC and is likely found in 20-30% of castration-resistant tumors compared to 5-10% at initial diagnosis.[12] Since this treatment-related NEPC is becoming more recognized and common and since it is very resistant to the conventional therapies of mCRPC, new therapies need to be developed for men with this disease.

Currently the standard of care for treating NEPC and its spectrum of diseases is to start with ADT as most NEPCs are mixed with adenocarcinoma. Once the cancer has become CRPC or if the histology at diagnosis was small cell prostate cancer (SCPC), the therapy tends to focus on using platinum combination therapy. Although there are no phase 3 trials looking at these therapies the literature shows that many patients have been treated with cisplatin and etoposide,[16-18] and a systematic review with a pooled-analysis using all available published material on NEPC patients found that chemotherapy had a statistically significant benefit for overall survival (hazard ratio (HR) 0.38 95% confidence interval (CI)(0.17-0.85)).[3] A large phase 2 trial at MD Anderson took men who fit the spectrum of NEPC and treated them with first line docetaxel which does have proven benefit in mCRPC and combined it with carboplatin as it was less toxic than cisplatin in combination.[14] The trial then treated them with combination cisplatin etoposide at first progression. Of the 113 men enrolled, 74 (65.4%) were progression free after 4 cycles of docetaxel/carboplatin and of the 71 patients that received second line therapy, 24 (33.8%) were progression free after 4 cycles. Using the same NEPC spectra as the previous trial, a randomized phase 2 trial randomized men with mCRPC stratified by NEPC or not to receive cabazitaxel with and without carboplatin. The trial found a PFS benefit in those men with NEPC of 5.7 mo versus 3.8 mo (P=0.009).[34] The other regimen that may be useful in NEPC patients is gemcitabine with oxaliplatin, and was tested in a phase 2 single arm trial with mCRPC men who failed docetaxel.[35] The trial included 33 men and demonstrated a PSA response rate of 55% and radiographic response rate of 82%. Although it did not comment on those with NEPC, this regimen deserves further study given the trend that other platinums are beneficial. Thus, although platinums appear to have a benefit in NEPC, none of them have been curative or led to long term remission in the vast majority of men.

In mCRPC platinums have been tested alone or in combination with other chemotherapies and the results have shown some dramatic successes with soft tissue response rates in the 70s and 80s in some studies while other have been in the teens.[19] Platinums act through DNA damage and it is conjectured that patients with inherited DNA-repair gene mutation, which is approximately 12% of metastatic prostate cancer,[20] or acquired DNA-repair gene mutations may benefit from them as shown in the TOPARP trial,[21] a single arm phase II trial that showed that patients with mCRPC that

had DNA-repair defects had better survival and response rates to olaparib a poly(adenosine diphosphate [ADP]-ribose) polymerase inhibitor.

3.2 Immune Checkpoint Blockade in Prostate Cancer

Immune checkpoint blockade is a novel systemic approach in which the patient's own immune system is stimulated to better recognize and destroy cancer cells. Ipilimumab is a monoclonal antibody and works by blocking the CTLA-4 receptor on T-cells during antigen presentation from a dendritic cell and leads to an inhibition of recognizing self from non-self. It thus stimulates more T-cells to target tumor cells that were evading the immune system. Ipilimumab was the first type of targeted immunotherapy that when compared to a novel melanoma vaccine showed a significant benefit in response rate including achieving complete responses and showed durable responses in metastatic melanoma.[23] Nivolumab, another monoclonal antibody, also acts to over stimulate the immune system and works by blocking the programed-death receptor-1 (PD-1) and prevents the binding of programed death ligand 1 and 2 (PD-L1/2). These ligands are presented on the surface of cells targeted by T-cells and when bound to PD-1 on the T-cells, results in halting immune destruction. Many cancers have evaded the immune system by overexpressing these ligands. Nivolumab was first definitively studied in melanoma patients in the first line setting by randomizing them to nivolumab versus decarbazine.[22] The results demonstrated a median PFS of 5.1 mo versus 2.2 mo (P<0.001) and a response rate of 40% versus 13.9% (P<0.001). Similar results were shown in another trial that randomized patients who had failed ipilimumab to nivolumab or treating physician's choice of chemotherapy.[36] Given the benefit of these individual therapies, a phase 1 trial was designed that randomized new metastatic melanoma patients to ipilimumab vs a combination nivolumab with ipilimumab. At the trial's end the median PFS was not reached in the combination group and was 4.4 mo in the ipilimumab alone group (P<0.001).[37] These results all show the benefit of immunotherapy in melanoma and now they are being studied in other cancer types.

Given the benefits of immune therapy in other cancer, ipilimumab was tested in patients with mCRPC against a placebo. Unfortunately the study did not show a clear survival benefit with p=0.053 when compared with placebo.[38] However since there appeared to be a synergy with androgen receptor blockers, a single arm phase II trial was done in men with mCRPC who progressed on enzalutamide using pembrolizumab with continuation of enzalutamide. An early report of this trial documented that 3 of 10 patients had a dramatic PSA reduction to ≤0.2 ng/mL.[39] Of these 3 patients, 2 had measureable disease at entry and both achieved a partial response.

Although the small cell histology is rare in prostate cancer, it is common in lung cancer. Small cell lung cancer (SCLC) like that of the prostate has a poor overall survival but if found early has the potential to be cured with a combination of chemotherapy with radiotherapy. However once it has become widespread, the prognosis is poor even with chemotherapy. Currently the mainstay of chemotherapy in SCLC is combination cisplatin with etoposide which is where SCPC got the direction to be treated by these agents given the similarity of histology. Recently a phase 1/2 trial was done that enrolled patients with progressive lung SCLC to nivolumab with and without ipilimumab in varying dose combinations.[24] The results demonstrated that the nivolumab alone arm had 15% with partial response and 22.5% with stable disease compared to 5% (1 patient) with a complete response, 20% with partial response, and 30% with stable disease in the combination arm. Not only were there responses in each arm, some appeared to be durable.

3.3 Study Agent

The active pharmaceutical ingredient in avelumab drug product is a fully human antibody (calculated molecular weight of 143832 Dalton) of the immunoglobulin G (IgG) 1 isotype that
specifically targets and blocks PD-L1, the ligand for PD-1, thus removing the suppressive effects of PD-L1 on the anti-tumor $CD8^+$ T cells. Avelumab drug product is a sterile, clear, and colorless concentrate for solution intended for intravenous (IV) infusion. The drug is presented at a concentration of 20 mg/mL in single-use glass vial containing 200 mg of avelumab. Avelumab drug product must be stored at 2°C to 8°C until use, and it must not be frozen. Rough shaking of avelumab product must be avoided. Avelumab drug product must be diluted with 0.9% saline solution; alternatively a 0.45% saline solution can be used if needed. It is recommended that the diluted avelumab solution is used immediately. If not used immediately, the diluted drug product can be stored up to 8 hours at room temperature or up to 24 hours at 2°C to 8°C. For further data on avelumab please refer to the current Investigator's Brochure.

3.3.1 Preclinical Experience

The nonclinical pharmacology studies have shown that avelumab functionally enhances T cell activation in vitro and significantly inhibits the growth of PD-L1 expressing tumors in vivo. Avelumab binds to human PD-L1 with a high affinity of 0.7 nM and not to any other B7 family proteins, and competitively blocks the interaction of PD-L1 with PD-1. The in vitro study results have shown that by binding to PD-L1, avelumab effectively enhances T cell activation as measured by interleukin-2 or interferon-gamma production. In addition, as a fully human IgG1 antibody, avelumab has the potential to trigger the antibody-dependent cell-mediated cytotoxicity (ADCC) against target cells expressing PD-L1. As a monotherapy, avelumab has demonstrated anti-tumor activity against murine MC38 colon carcinoma tumors that are characterized by a high level of PD-L1 expression. A dose-dependent trend was observed, and 400 μg per dose (20 mg/kg, approximately) was identified as the optimally effective dose when given every third day for 3 total doses. The in vivo anti-tumor effects were found to be primarily mediated by CD8+ T cells as evidenced by the observation that in vivo depletion of this cell type completely abrogated the anti-tumor efficacy of avelumab. The contribution of ADCC as a potential mechanism of anti-tumor activity was further demonstrated in vivo using a deglycosylated version of avelumab to abrogate fragment crystalline receptor binding or via the systemic depletion of natural killer (NK) cells. In both settings, loss of in vivo ADCC potential significantly reduced the anti-tumor activity.

The combination of avelumab with commonly used cancer treatments, such as cytotoxic agents and radiation therapy, resulted in an improved anti-tumor activity. Chemotherapy with combination therapy (with folinic acid, 5-fluorouracil, and oxaliplatin [FOLFOX], and radiation therapy showed the better tumor growth inhibition. In particular, radiation therapy was found to be a highly synergistic combination with avelumab capable of causing complete regression of established tumors probably through generating anti-tumor immune memory. Various immunomonitoring assays were incorporated into the in vivo studies. Treatment with avelumab resulted in a consistent increase in the percentage of CD8+PD-1+ T cells and an increased frequency of CD8+ T cells with an effector memory (TEM) phenotype as determined by flow cytometry. Furthermore, these changes correlated with the anti-tumor effect. Increases in tumor antigen-specific T cell responses, as measured by enzyme-linked immunosorbent spot and pentamer immunoassays, were evident following treatment with avelumab and these responses were enhanced when combined with FOLFOX or radiation. Hence, increases in $CD8^+PD\text{-}1^+$ T cells, CD8+ TEM cells, and antigen-specific T cell

responses, may be leveraged as pharmacodynamics (PD) biomarkers with translational relevance to the clinical setting. For further data, please refer to the current Investigator's Brochure for avelumab.

3.3.1.1 Preclinical Pharmacokinetics and Metabolism

Full pharmacokinetic (PK) profiles were evaluated in mice and cynomolgus monkeys, since these species have similar binding affinity to PD-L1 to humans, and therefore these species are likely to have similar target-mediated clearance. Additional toxicokinetic (TK) data were obtained during the course of repeated toxicity studies with avelumab in mice, rats, and cynomolgus monkeys, with molecules MSB0010294 and MSB0010682 being the precursors to the final molecule avelumab. The anti-PD-L1 antibodies from research batches and precursor molecules tested in single-dose PK studies in mice and cynomolgus monkeys demonstrated pronounced nonlinear PK characteristics in mice and cynomolgus monkeys in single-dose studies at doses below 20 mg/kg, suggesting a combination of first order catabolic clearance and saturable target-mediated clearance. Similar terminal half-lives (t1/2) ranging from 58 to 70 hours at doses between 20 and 140 mg/kg were observed in toxicity studies in mice and monkeys.

Since avelumab represents a foreign protein to the immune system of animals, anti-avelumab antibodies in rodents and nonhuman primates were observed and have been considered in interpreting the nonclinical data, with higher doses generally resulting in lower immunogenicity incidence. This is potentially due to the interference of avelumab trough concentrations with the measurement of antidrug antibody (ADA), and did not affect exposure or impact the conclusions of the toxicity studies. The immunogenicity incidence against the human antibody avelumab in animals is not deemed predictive for human subjects. The clearance from the clinical population PK model is well predicted by allometric scaling from the cynomolgus monkey, confirming its suitability as the primary nonclinical PK species.

For further data, please refer to the current Investigator's Brochure for avelumab.

3.3.1.2 Preclinical Toxicology

The toxicological profile of avelumab was evaluated in vivo in mice, rats, and cynomolgus monkeys. In addition, in vitro cytokine release assays (CRA) in human and cynomolgus monkey whole blood and peripheral blood mononuclear cells (PBMCs) as well as tissue cross reactivity (TCR) studies in normal human and cynomolgus monkey tissues were performed.

On the basis of the binding affinity data, the cynomolgus monkey and the mouse were selected as relevant species for the nonclinical safety testing of avelumab. In repeat dose toxicity studies in CD-1 mice with avelumab IV bolus injections, mortality occurred mainly after the 3rd administration. Due to severe post-dose anaphylactic reactions after repeated administration of avelumab in mice and the low binding affinity in rats, rodent species are not considered appropriate for nonclinical safety testing of avelumab and therefore, a single species approach (cynomolgus monkey only) was followed and confirmed with Health Authorities.

In cynomolgus monkeys neither in the pilot 4-week IV repeat-dose toxicity study nor in the pivotal 13-week study, clinical signs of hypersensitivity or avelumab-related infusion reactions have been

seen after repeated treatment with avelumab at dose levels of 20, 60, and 140 mg/kg, respectively. For the pilot 4-week study as well as for the pivotal 13-week IV repeat-dose toxicity study, a no observed adverse effect level (NOAEL) of 140 mg/kg for systemic toxicity was established.

No reproductive toxicity studies were conducted. However, the reproductive and developmental toxicity potentially associated with avelumab treatment is considered adequately established based on available data, from repeat-dose studies and public sources and in view of the pursued indications and targeted indications (life threatening cancer diseases, advanced-stage cancer subjects). Considering that disruption of PD-1/PD-L1 communication has been reported to significantly increase the risk of fetal loss during pregnancy, the potential for adverse outcomes on embryofetal development cannot be excluded and adequate protections must be in place to prevent risk of pregnancies.

Initial CRA in human and cynomolgus monkey whole blood and PBMCs revealed no clear-cut evidence for release of pro-inflammatory cytokines. However, a subsequent, optimized CRA demonstrated evidence of potential cytokine release in phytohemagglutinin (PHA) prestimulated PBMCs. There was no evidence of phototoxicity on evaluation of UV absorption. Overall, the nonclinical safety profile established for avelumab is considered adequate to support the use of avelumab in the planned therapeutic indication in humans. For further data, please refer to the current Investigator's Brochure for avelumab.

3.3.2 Clinical Experience

Avelumab is currently in clinical development across Phases I, II, and III. We have highlighted the following 4 clinical trials:

- EMR 100070-001: A Phase I, open-label, multiple ascending dose trial to investigate the safety, tolerability, pharmacokinetics, biological and clinical activity of avelumab in subjects with metastatic or locally advanced solid tumors and expansion to selected indications
- EMR 100070-002: A Phase I trial to investigate the tolerability, safety, pharmacokinetics, biological and clinical activity of avelumab in Japanese subjects with metastatic or locally advanced solid tumors, with expansion part in Asian subjects with gastric cancer
- EMR 100070-003: A Phase II, single arm, open-label, multicenter trial to investigate the clinical activity and safety of avelumab in subjects with Merkel cell carcinoma (MCC)
- EMR 100070-004: A Phase III open-label, multicenter trial of avelumab versus docetaxel in subjects with non-small cell lung cancer that has progressed after a platinum-containing doublet

EMR 100070-001 is a Phase I, open-label, multiple ascending dose trial to investigate the safety, tolerability, PK, biological and clinical activity of avelumab in subjects with metastatic or locally advanced solid tumors and expansion to selected indications. This trial consists of 2 parts. In the dose escalation part, sequential cohorts of subjects were enrolled at progressively higher dose levels (ranging from 1.0, 3.0, 10.0, and 20.0 mg/kg once every 2 weeks) with a 3 + 3 algorithm design for determination of the maximum tolerated dose (MTD) of avelumab; in the treatment expansion phase, subjects in different tumor cohorts are being treated with 10 mg/kg of avelumab once every 2 weeks until, confirmed progression, unacceptable toxicity, or any reason for withdrawal occurs. More than 1500 subjects have been enrolled in the EMR 100070-001 trial. The 3 + 3 dose escalation

algorithm to determine the MTD is complete and a dose of 10 mg/kg once every 2 weeks was determined for the tumor expansion cohorts on the basis of safety, PK, and PD observations. The treatment expansion part of the trial consists of 16 tumor treatment cohorts. As of 09 June 2016, 53 subjects in the dose escalation part had received avelumab (4, 13, 15, and 21 subjects had received 1.0, 3.0, 10.0, and 20.0 mg/kg of avelumab, respectively) and 1738 subjects in the pooled safety dataset part (Study EMR100070-001 and EMR100070-003 Part A) had received 10 mg/kg avelumab.

Most of the observed adverse events (AEs) were either in line with those expected in subjects with advanced solid tumors or with class effects of monoclonal antibody blocking of the PD-1/PD-L1 axis. Infusion-related reactions including drug hypersensitivity reactions and immune-mediated adverse reactions have been identified as important risks for avelumab. Respective risk mitigation measures have been implemented in all ongoing clinical studies with avelumab.

EMR 100070-004 is an ongoing phase III, open-label trial with a primary objective of demonstrating superiority with regard to OS of avelumab versus docetaxel in subjects with PD-L1 positive NSCLC after failure of a platinum-based doublet. As of 17 December 2016, safety data can only be presented in a blinded manner, meaning that an assessment to study medication (avelumab or docetaxel) is not possible. Overall, a total of 533 SAEs (385 cases) have been reported at the data cutoff of 17 December 2016. Of those SAEs, 416/533 (298 cases) were reported in subjects receiving any study medication. From these 416 SAEs 146 SAEs (111 cases) were reported as treatment related.

On March 23, 2017 the FDA announced that avelumab injection 20 mg/mL, for intravenous use, has been approved for treatment of adults and pediatric patients 12 years and older with metastatic Merkel cell carcinoma.

For further data, please refer to the current Investigator's Brochure for avelumab.

3.3.2.1 Pharmacokinetics

Pharmacokinetic assessments have been performed in ongoing Trials EMR 100070-001 and EMR 100070-002. The results are based on the data available as of 19 May 2015 (Trial EMR 100070-001) and 13 October 2014 (Trial EMR 100070-002).

Pharmacokinetics following the first 1-hour infusion and dose proportionality of avelumab have been characterized in 77 mainly Caucasian subjects treated in the dose escalation and expansion cohort of the Phase I Trial EMR 100070-001 by standard non-compartmental analysis based on rich serum concentration-time data obtained over a complete dosing interval of 2 weeks (= tau). The exposure parameters maximum concentration (Cmax) and area under the concentration-time curve (AUC) after first dose generally increased in an approximately dose-proportional manner in the range between 3 to 20 mg/kg). The concentration at the end of dose interval (Cmin) increased proportionally with dose between 10 to 20 mg/kg, but more than proportionally for doses between 1 to 10 mg/kg. The total systemic clearance was low, 0.37 mL/h/kg ± 0.11 mL/h/kg at the 10 mg/kg dose (n=40).

The terminal half-life increased with the dose. However, the average values were 102 hours (4.3 days) and 120 hours (5.0 days) for 10 mg/kg and 20 mg/kg doses, respectively, with no significant difference between these two dose groups.

PK appears to be similar across different tumor types. The trough concentrations from cohorts with different tumor types were in a similar range, consistent with those obtained in the all-comer tumor patients in the dose escalation cohort who received the 10 mg/kg dose and had a serial PK sampling (Cmin in the dose escalation cohorts is 22 ± 12 and 25 ± 16 µg/mL for Day 15 and Day 29, respectively). A preliminary analysis of the PK data was performed based on the serum concentration (as of 13 October 2014) of avelumab obtained from 5 Japanese subjects treated with 3 mg/kg, 6 Japanese subjects treated with 10 mg/kg and 6 Japanese subjects treated with 20mg/kg as a 1-hour IV infusion once every 2 weeks. Preliminary non-compartmental PK parameter calculation was performed based on non-QA concentrations obtained during the first infusion using scheduled sample collection times and an infusion duration of 1 hour. Exposure values Cmax and AUC increased almost proportional with dose. For the 10 mg/kg dose, the total systemic clearance was low (0.45 mL/h/kg ± 0.20 mL/h/kg). Mean trough levels obtained immediately before next infusion and mean peak levels obtained immediately after infusion end (at Days 15, 29, 43 and 85) remained at fairly constant levels indicating no accumulation following multiple infusions. This result is in line with the calculated apparent $t_{1/2}$ and the applied dosing scheme (once every 2 weeks) and is similar to that reported in Trial EMR 100070-001.

Trial EMR 100070-001 is a global trial performed mainly in Caucasian subjects while Trial EMR 100070-002 is performed exclusively in Japan. The preliminary concentrations obtained over time and the clearance during the first dosing interval was similar in Japanese and Caucasian subjects. This was confirmed during the population PK analysis. Population PK analysis was performed based on data of 410 subjects from ongoing Trials EMR 100070-001 and EMR 100070-002. Eighty-three subjects with rich PK profiles, 9 subjects with peak and trough concentrations and 318 subjects with only trough concentrations were included in this analysis. In order to describe the non-linear PK at low concentration levels, presumably due to target mediated elimination, a 2 compartment model with mixed linear plus Michaelis-Menten elimination was evaluated. Limited by very few observations collected in low concentration range showing non-linear elimination, the estimation precision of Michaelis-Menten elimination was rather poor (Maximal elimination (Vmax)=0.07 mg/h [relative standard error=94%], Michaelis-Menten constant (Km)=0.9 ug/mL [relative standard error=448%]). The additional non-linear elimination component did not improve the overall data fitting at the statistical significance of p-value below 0.01. Covariate multivariate relationships including body weight, body surface area, lean body mass, age, gender, race, creatinine clearance, serum albumin, serum bilirubin, aspartate transaminase, alanine transaminase, and tumor type were explored. Serum albumin was found to significantly correlate (negatively) with clearance with an effect size on AUC ranging from -41% to 27%, which corresponds to serum albumin level ranging from 18 g/L to 52 g/L. Lean body mass was found to significantly correlate (positively) with the central volume of distribution with effect size ranging from -23% to 33%, which corresponds to lean body mass ranging from 29.75 kg to 80.92 kg. The clearance of male subjects was found to be 14% higher than of female subjects. This finding may be explained by the correlation between gender and lean body mass, the latter of which showed a weaker (and small) covariate effect to the clearance when gender effect was not considered. It is to be further investigated as new data accumulate. No other covariate effect reached statistical significance (at a pre-set p-value of 0.001). Neither body weight, nor body surface area nor lean body mass was found to be significantly

correlated to the clearance. Additional analysis is planned to further confirm these preliminary findings.

In order to determine the levels of anti-PD-L1 target occupancy (TO) towards PD-L1 on CD3+ T lymphocytes at the end of the dosing interval, blood samples were taken at Cmin after the first dose (Day 15) in a small number of subjects during the initial dose escalation part of Trial EMR 100070-001 (n=3 at the 1 mg/kg dose, n=2 at the 3 mg/kg dose, and n=4 at the 10 mg/kg dose). After the 10 mg/kg dose, TO was greater than 90% at the end of the dosing interval at avelumab trough serum levels ranging between 12.69 to 26.87 µg/mL. After the 3 mg/kg dose, TO also exceeded 90%, at trough drug concentrations of 4.56 and 6.99 µg/mL. After the 1 mg/kg dose, 2 out of 3 subjects displayed less than 90% TO at trough serum concentrations, which were below the quantification limit of 0.2 µg/mL in these 2 subjects.

Earlier studies showed a concentration of 1 µg/mL avelumab was required in whole blood to reach a target saturation plateau of >95% TO. The population PK analysis showed non-linear Michaelis-Menten elimination of avelumab at very low serum concentrations with a Vmax=0.07 mg/h and a Km=0.9 µg/mL. Despite the large imprecision obtained, these results are consistent with the in vitro blood concentrations required to achieve target saturation. Based on these analysis and trough serum levels of the drug observed in the dose escalation cohorts in EMR 100070-001, TO would reach or exceed > 95% occupancy throughout the entire dosing interval for 10 out of 13 subjects who received 3 mg/kg, and for all (15/15) subjects who received 10 mg/kg, in the dose escalation group in Trial EMR 100070-001. Thus, it appears that a 10 mg/kg dose of avelumab would achieve maximal TO in blood in the majority of subjects based on in vitro studies. Therefore, in order to achieve target saturation during the whole treatment period in the majority of subjects, the dose of 10 mg/kg every 2 weeks was selected as the dose for further investigation in treatment expansion cohorts in the Phase I Trial EMR 100070-001 and for future Phase III studies.

For further data, please refer to the current Investigator's Brochure for avelumab.

3.3.2.2 Efficacy

The clinical efficacy information summarized here includes data from the NSCLC and ovarian cancer expansion cohorts of the ongoing Phase I Trial EMR 100070-001, the 20 subjects in the gastric cancer expansion cohort of the ongoing Phase I Trial EMR 100070-002, and the 88 patients in the Phase II EMR 100070-003 Trial in Merkel Cell carcinoma.

The NSCLC expansion cohort in the ongoing Phase I Trial EMR 100070-001 had a cutoff date of 15 January 2015, 6 months after start of avelumab treatment of the last subject in this expansion cohort (a total of 184 treated subjects).[25] The objective response rate (ORR) based on confirmed and unconfirmed responses for subjects treated in the NSCLC expansion cohort was 14.1% (26 of 184 NSCLC subjects). Progression free survival (PFS) and overall survival (OS) were all evaluated for all NSCLC subjects treated in the expansion phase. As of 15 January 2015, the median PFS and OS for the NSCLC treatment expansion cohort were 11.6 weeks and 8.4 months, respectively. A total of 142 out of the 184 subjects in the second-line NSCLC expansion cohort provided tumor samples that were evaluable for PD-L1 expression. Antitumour activity was seen in tumors defined as PD-L1+ and PD-L1− using prespecified PD-L1 expression levels on tumour cells (1%, 5%, and 25%) and tumour-

associated immune cells. In patients with PD-L1+ vs PD-L1− tumours, there was no significant difference in response rates or OS, whereas PFS was longer in those patients with PD-L1+ tumours compared with PD-L1− tumours in an analysis based on a 1% cut-off for tumour cell staining (hazard ratio for progressive disease, 0.45; 95% CI: 0.27, 0.75).

The ovarian cancer expansion cohort had a data cutoff of 23 October 2015. This cohort enrolled and treated a total of 124 subjects. The ORR based on confirmed and unconfirmed responses for subjects treated in the ovarian cancer expansion cohort was 9.7% (12 of 124 subjects). In 6 of the 12 responders (50.0%), the responses were ongoing at the time of the data cutoff. The median PFS for the ovarian cancer expansion cohort was 11.3 weeks (95% CI: 6.1 to 12.0 weeks).

The gastric cancer expansion cohort in the ongoing Phase I Trial EMR100070-002 had a data cut off of 11 March 2015 for 20 subjects being treated with 10 mg/kg of avelumab once every 2 weeks. As of the data cutoff, 3 of 20 subjects responded to study treatment (all responses were PRs and all responses were confirmed responses), and the BOR was 15.0% (95% CI: 3.2% to 37.9%). Two of the responders had the first response at around Week 6 and 1 responder had the first response at around Week 18. Two of the 3 responders had their response continued at the time of the data cutoff. The median PFS of this group according to RECIST 1.1 was 11.9 weeks (95% CI: 6.0 to 12.3 weeks). The Kaplan-Meier estimates predicted a PFS rate of 43.3% at 12 weeks.

The Phase II EMR 100070-003 Trial in Merkel Cell carcinoma gave avelumab to 88 patients and resulted in an objective response in 28 patients (31.8% [95.9% CI 21.9-43.1]), including 8 complete responses.[27] Responses were ongoing in 23 (82%) of 29 at the time of data cut off 03 March 2016. Median PFS was 2.7 months (95% CI: 1.4, 6.9), and the proportion of subjects who were progression-free at 6 months was 40% (95% CI: 29, 50).

For further data, please refer to the current Investigator's Brochure for avelumab.

3.4 Purpose and Rationale

Data supporting PD-L1 inhibition in prostate cancer was found when enzalutamide resistant cell lines and xenografts on mice had increased PD-L1.[28] Our own cell lines established at Duke that are enzalutamide resistant also demonstrate upregulation of PD-L1 at the protein and RNA level as compared with the parental cell lines, suggesting that PD-L1 is an adaptive response to stress and is highly dynamic (data unpublished). Further, we have also looked at a cohort of patients with NEPC/SCPC using a tissue microarray for PD-L1 expression by immunohistochemistry and have found that a small subset (~20% small cell, ~10% adenocarcinoma) of these cases express high levels of PD-L1 (data unpublished). Further still is evidence showing that there is a high burden of genetic mutations in NEPC[15] which has been seen in other cancers to confer susceptibility to immunotherapy.

Given the emerging role of immunotherapy across multiple tumor types to produce durable responses, and given the similarity of small cell by both histology and its response to current chemotherapy, we hypothesize that avelumab will produce a clinical and radiographic response in NEPC that will be durable in a subset of patients. In this study, we are defining the NEPC "phenotype"

based on clinical poor risk features of AR-independence or based on histologic evidence of NEPC in tissue or serum.

4 OBJECTIVES AND ENDPOINTS

4.1 Primary Endpoint

To determine the efficacy of PD-L1 inhibition with avelumab as measured by a modified PCWG3, where RECIST 1.1 is replaced with iRECIST, a modified RECIST 1.1 for immune-based therapeutics, radiographic response rate in men with metastatic neuroendocrine-like prostate cancer.

4.2 Secondary Endpoints

1. To describe the efficacy of PD-L1 inhibition with avelumab as measured by PCWG3 using RECIST1.1
2. To describe the radiographic progression free survival (rPFS) of PD-L1 inhibition with avelumab using modified PCWG3 with both RECIST 1.1 and iRECIST criteria in this setting.
3. To describe the overall survival of PD-L1 inhibition in this setting.
4. To described the toxicities and safety of PD-L1 inhibition with avelumab in men with metastatic neuroendocrine-like prostate cancer.

4.3 Exploratory Endpoints

1. To describe the impact of PD-L1 inhibition with avelumab on blood-based biomarker changes over time, including PSA, chromogranin-A, cell free DNA, LDH, and alkaline phosphatase.
2. To determine if levels of circulating biomarkers secreted by neuroendocrine-like prostate cancers correlate with clinical and radiographic treatment response
3. To determine if the presence of different immunohistochemical markers on the pre-biopsy specimens prognosticates clinical and radiographic treatment response
4. To determine if the level of different circulating immune cells correlate with both progressive addition of immunotherapy as well as clinical and radiographic treatment response or disease progression
5. To determine if levels of cell free DNA correlate with clinical and radiographic treatment response
6. To isolate prostate neuroendocrine-like CTCs for ex vivo growth and culture and characterization studies.

5 INVESTIGATIONAL PLAN

5.1 Study Design

This is an open label, single arm, phase 2 study of men with neuroendocrine phenotype prostate cancer to assess the safety and efficacy of avelumab 10 mg/kg IV every 2 weeks until progression or intolerable side effects. Cycles will be 4 weeks long and thus include 2 doses of avelumab. This study will be at multiple centers with the Duke Cancer Institute as the lead site. For stage 1, Duke will serve as the single site for this study. For stage 2, the study would be expanded to include additional sites

through the Department of Defense Prostate Cancer Clinical Trials Consortium (DOD PCCTC). All subjects will be followed for disease progression and death from the date that the subjects were registered to the protocol.

At radiologic progression a standard of care post-treatment progression biopsy will be collected at the discretion of the treating provider, and if proper consent is obtained, additional tissue will be collected for research tests including assessments of resistance mechanisms and immune checkpoint status. The additional research tissue will be banked in the Biospecimen Repository & Processing Core (BRPC) under Pro00080869. The study team will also pursue dual consent to BRPC Pro00035974 for future unspecified research.

Men will continue on their ADT used at entry into study per investigator with subsequent changes made per investigator. Men not on ADT at time of entry due to being purely SCPC can remain off ADT. Men with SCPC on ADT at study entry can remain on ADT per investigator while all men with mixed histologies should remain on active ADT during trial participation.

Men will be allowed to receive palliative radiation to any disease site indicated by the treating physician at any time before or during the study, provided that another untreated site of measureable disease is present at baseline.

5.2 Drug Discontinuation Criteria

All subjects will be monitored for adverse events (AEs) on treatment using NCI CTCAE v4.0 or the most current version. Stopping rules based on unacceptable toxicities will be used in this study. Avelumab will be discontinued in the patient if there is unacceptable toxicity defined as:

- Any grade 5 treatment-related death
- Any Grade 4 AE except for single laboratory values out of normal range that are unlikely related to study treatment as assessed by the Investigator, do not have any clinical correlate, and resolve within 7 days with adequate medical management
- Any Grade 3 AE except for any of the following:
    - Transient (≤ 6 hours) Grade 3 flu-like symptoms or fever, which is controlled with medical management
    - Transient (≤ 24 hours) Grade 3 fatigue, local reactions, headache, nausea, emesis that resolves to Grade ≤ 1
    - Single laboratory values out of normal range (excluding Grade ≥ 3 liver function test increase) that are unlikely related to study treatment according to the Investigator, do not have any clinical correlate, and resolve to Grade ≤ 1 or baseline within 7 days or by the next visit with adequate medical management
    - Tumor flare phenomenon defined as local pain, irritation, or rash localized at sites of known or suspected tumor
    - Change in Karnofsky Performance Status to $\underline{\leq}$ 40 that does not resolve to $\underline{\geq}$ 50 within 14 days (infusions should not be given on the following cycle, if the Karnofsky Performance Status is $\underline{\leq}$ 40 on the day of study drug administration)

Grade 2 immune-related AEs should be managed as follows:

- If a Grade 2 ADR resolves to Grade ≤ 1 by the last day of the current cycle, treatment may continue.

- If a Grade 2 ADR does not resolve to Grade ≤ 1 by the last day of the current cycle, infusions should not be given on the following cycle. If at the end of the following cycle the event has not resolved to Grade 1, the subject should permanently discontinue treatment with a avelumab ADR (except for hormone insufficiencies and conditions that are adequately treated with medical management, that can be managed by replacement therapy; for these hormone insufficiencies, up to 2 subsequent doses may be omitted). Patients with transient, minor Grade 2 ADRs, may be permitted to continue therapy with permission of the study PI provided the patient is adequately managed medically.
- Upon the second occurrence of the same Grade 2 ADR (except for hormone insufficiencies that can be managed by replacement therapy) in the same subject, treatment with avelumab has to be permanently discontinued

There will be no dose modifications for avelumab in this study. Dose interruptions for reasons other than toxicity (e.g., surgical procedures) may be allowed with PI approval. The investigator and the PI will determine the acceptable length of treatment interruption. If avelumab is withheld for > 8 weeks then study treatment will be permanently discontinued.

If the investigator believes the patient is likely to derive clinical benefit, avelumab treatment can be resumed after being withheld for > 8 weeks. If a patient must be tapered off corticosteroids used to treat adverse events, study treatment may be withheld for > 8 weeks with PI approval.

5.3 Trial Stopping Rules

If at any time after the first 12 subjects are enrolled, the observed proportion of unacceptable treatment-related toxicity exceeds 25% by at least one standard error, accrual will be immediately suspended to the trial. Unacceptable toxicity will be defined as grade 3 or higher treatment related adverse events. Each patient will be categorized according to their most severe toxicity using NCI CTC v4.0 or the most current version.

5.4 Treatment Modification Guidelines for Infusion-Related Reactions

Please see the below table for suggested treatment modification for symptoms of infusion related reactions

NCI-CTCAE Grade (modified)	Treatment Modification for Study Drug
Grade 1 – mild Mild transient reaction; (based on combination of signs and symptoms which may include mild pruritus, flushing, rhinitis, rash, fever, and chills)	Stop study drug infusion and provide supportive care in accordance with local institutional hypersensitivity protocol. Resume infusion at 50% of previous rate once acute infusion-related reaction has resolved and monitor closely for any worsening.
Grade 2 – moderate Therapy or infusion interruption indicated but responds promptly to symptomatic treatment (for example, antihistamines,	Stop study drug infusion and provide supportive care in accordance with local institutional hypersensitivity protocol.

NSAIDs, narcotics, IV fluids); prophylactic medications indicated for ≤ 24 h.	Resume infusion at 50% of previous rate once infusion-related reaction has resolved or decreased to at least Grade 1 in severity, and monitor closely for any worsening.
Grade 3 or Grade 4 – severe or life-threatening Grade 3: Prolonged (for example, not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for clinical sequelae. Grade 4: Life-threatening consequences; urgent intervention indicated.	Stop the study drug infusion immediately and disconnect infusion tubing from the subject. Subjects have to be withdrawn immediately from study drug treatment and must not receive any further study drug treatment.
• If hypersensitivity reaction occurs, the subject must be treated according to the best available medical practice. • Once the avelumab infusion rate has been decreased by 50% or interrupted due to an infusion-related reaction (grade 1 or 2), the infusion rate may be increased back to the initial rate during that same infusion or during subsequent infusions at the discretion of the provider. Subjects may also be pre-medicated with steroids and/or oral or inhaled cromolyn sodium at the discretion of the provider. • For subsequent infusions after a grade 1 or 2 reaction, at least 1 modification must be made to the infusion parameters: rate can be decreased (to a 3 or 4 hour infusion) and/or additional pre-medications can be administered at the discretion of the provider. • The starting infusion rate for the study drug should not exceed 4 hours. • If the avelumab is given over 4 hours, the options for optimization of pre-medications have been exhausted, and the patient continues to experience a grade 1 or 2 reaction, then the study drug must be discontinued permanently.	

5.5 Management of Immune-mediated Adverse Reactions

Please see the table below for management of immune-mediated adverse reactions

Since inhibition of PD-L1 stimulates the immune system, immune-related AEs (irAEs) may occur. Treatment of irAEs is mainly dependent upon severity (NCI-CTCAE grade): Grade 1 to 2: treat symptomatically or with moderate dose steroids, more frequent monitoring Grade 1 to 2 (persistent): manage similar to high grade AE (Grade 3 to 4) Grade 3 to 4: treat with high dose corticosteroids Treatment of gastrointestinal, dermatological, pulmonary, hepatic and endocrine irAEs should follow guidelines set forth in the table below.		
Gastrointestinal irAEs		
Severity of Diarrhea / Colitis (NCI-CTCAE v4.03)	**Management**	**Follow-up**

Grade 1 Diarrhea: < 4 stools/day over Baseline Colitis: asymptomatic	Continue avelumab therapy Symptomatic treatment (for example, loperamide)	Close monitoring for worsening symptoms Educate subject to report worsening immediately If worsens: Treat as Grade 2 or 3/4
Grade 2 Diarrhea: 4 to 6 stools per day over Baseline; IV fluids indicated < 24 hours; not interfering with ADL Colitis: abdominal pain; blood in stool	Delay avelumab therapy Symptomatic treatment	If improves to Grade 1: Resume avelumab therapy If persists > 5 to 7 days or recur: 0.5 to 1.0 mg/kg/day methylprednisolone or equivalent When symptoms improve to Grade 1, taper steroids over at least 1 month, consider prophylactic antibiotics for opportunistic infections, and resume avelumab therapy per protocol (if reduced to 10 mg/day or less of prednisone equivalent). If worsens or persists > 3 to 5 days with oral steroids: Treat as Grade 3 to 4
Grade 3 to 4 Diarrhea (Grade 3): ≥ 7 stools per day over Baseline; incontinence; IV fluids ≥ 24 hrs.; interfering with ADL Colitis (Grade 3): severe abdominal pain, medical intervention indicated, peritoneal signs Grade 4: life-threatening, perforation	Discontinue avelumab therapy per protocol 1.0 to 2.0 mg/kg/day methylprednisolone IV or equivalent Add prophylactic antibiotics for opportunistic infections Consider lower endoscopy	If improves: Continue steroids until Grade 1, then taper over at least 1 month If persists > 3 to 5 days, or recurs after improvement: Add infliximab 5 mg/kg (if no contraindication), Note: Infliximab should not be used in cases of perforation or sepsis
Dermatological irAEs		
Grade of Rash (NCI-CTCAE v4)	**Management**	**Follow-up**

Grade 1 to 2 Covering ≤ 30% body surface area	Symptomatic therapy (for example, antihistamines, topical steroids) Continue avelumab therapy	If persists > 1 to 2 weeks or recurs: Consider skin biopsy Delay avelumab therapy Consider 0.5 to 1.0 mg/kg/day methylprednisolone IV or oral equivalent. Once improving, taper steroids over at least 1 month, consider prophylactic antibiotics for opportunistic infections, and resume avelumab therapy once patient has reached prednisone equivalent of 10 mg/d and improving. If worsens: Treat as Grade 3 to 4
Grade 3 to 4 Covering > 30% body surface area; life threatening consequences	Delay or discontinue avelumab therapy Consider skin biopsy Dermatology consult 1.0 to 2.0 mg/kg/day methylprednisolone IV or IV equivalent	If improves to Grade 1: Taper steroids over at least 1 month and add prophylactic antibiotics for opportunistic infections Resume avelumab therapy
Pulmonary irAEs		
Grade of Pneumonitis (NCI-CTCAE v4)	**Management**	**Follow-up**
Grade 1 Radiographic changes only	Consider delay of avelumab therapy Monitor for symptoms every 2 to 3 days Consider Pulmonary and Infectious Disease consults	Re-image at least every 3 weeks If worsens: Treat as Grade 2 or Grade 3 to 4

Grade 2 Mild to moderate new symptoms	Delay avelumab therapy Pulmonary and Infectious Disease consults Monitor symptoms daily, consider hospitalization 1.0 mg/kg/day methyl-prednisolone IV or oral equivalent Consider bronchoscopy, lung biopsy	Re-image every 1 to 3 days If improves: When symptoms return to near Baseline, taper steroids over at least 1 month and then resume avelumab therapy and consider prophylactic antibiotics If not improving after 2 weeks or worsening: Treat as Grade 3 to 4
Grade 3 to 4 Severe new symptoms; New / worsening hypoxia; life-threatening	Discontinue avelumab therapy Hospitalize Pulmonary and Infectious Disease consults 2 to 4 mg/kg/day methylprednisolone IV or IV equivalent Add prophylactic antibiotics for opportunistic infections Consider bronchoscopy, lung biopsy	If improves to Baseline: Taper steroids over at least 6 weeks If not improving after 48 hours or worsening: Add additional immunosuppression (for example, infliximab, cyclophosphamide, IV immunoglobulin, or mycophenolate mofetil)
Hepatic irAEs (reportable per section 9.3)		
Grade of Liver Test Elevation (NCI-CTCAE v4)	**Management**	**Follow-up**
Grade 1 Grade 1 AST or ALT > ULN to 3.0 x ULN and / or total bilirubin > ULN to 1.5 x ULN	Continue avelumab therapy	Continue liver function monitoring If worsens: Treat as Grade 2 or 3 to 4
Grade 2 AST or ALT > 3.0 to ≤ 5 x ULN and / or total bilirubin > 1.5 to ≤ 3 x ULN	Delay avelumab therapy Increase frequency of monitoring to every 3 days	If returns to Baseline: Resume routine monitoring, resume avelumab therapy If elevations persist > 5 to 7 days or worsen:

	Report per section 9.3	0.5 to 1 mg/kg/day methylprednisolone or oral equivalent and when LFT returns to Grade 1 or Baseline, taper steroids over at least 1 month, consider prophylactic antibiotics for opportunistic infections, and resume avelumab therapy
Grade 3 to 4 AST or ALT > 5 x ULN and / or total bilirubin > 3 x ULN	Discontinue avelumab therapy Increase frequency of monitoring to every 1 to 2 days 1.0 to 2.0 mg/kg/day methylprednisolone IV or IV equivalent Add prophylactic antibiotics for opportunistic infections Consult gastroenterologist Consider obtaining MRI/CT scan of liver and liver biopsy if clinically warranted Report per section 9.3	If returns to Grade 2: Taper steroids over at least 1 month If does not improve in > 3 to 5 days, worsens or rebounds: Add mycophenolate mofetil 1 gram (g) twice daily If no response within an additional 3 to 5 days, consider other immunosuppressants per local guidelines
Endocrine irAEs		
Endocrine Disorder	**Management**	**Follow-up**
Asymptomatic TSH abnormality	Continue avelumab therapy If TSH < 0.5 x LLN, or TSH > 2 x ULN, or consistently out of range in 2 subsequent measurements: include T4 at subsequent cycles as clinically indicated; consider endocrinology consult	
Symptomatic endocrinopathy	Evaluate endocrine function Consider pituitary scan Symptomatic with abnormal lab / pituitary scan:	If improves (with or without hormone replacement): Taper steroids over at least 1 month and consider prophylactic antibiotics for opportunistic infections Resume avelumab therapy

	Delay avelumab therapy 1 to 2 mg/kg/day methylprednisolone IV or by mouth equivalent Initiate appropriate hormone therapy No abnormal lab / pituitary MRI scan but symptoms persist: Repeat labs in 1 to 3 weeks / MRI in 1 month	Subjects with adrenal insufficiency may need to continue steroids with mineralocorticoid component
Suspicion of adrenal crisis (for example, severe dehydration, hypotension, shock out of proportion to current illness)	Delay or discontinue avelumab therapy Rule out sepsis Stress dose of IV steroids with mineralocorticoid activity IV fluids Consult endocrinologist If adrenal crisis ruled out, then treat as above for symptomatic endocrinopathy	
Cardiac irAEs		
Myocarditis	Management	Follow-up
New onset of cardiac signs or symptoms and / or new laboratory cardiac biomarker elevations (e.g. troponin, CK-MB, BNP) or cardiac imaging abnormalities suggestive of myocarditis.	Withhold avelumab therapy Hospitalize. In the presence of life threatening cardiac decompensation, consider transfer to a facility experienced in advanced heart failure and arrhythmia management. Cardiology consult to establish etiology and rule-out immune-mediated myocarditis. Guideline based supportive treatment as appropriate per cardiology consult.* Consider myocardial biopsy if recommended per cardiology consult.	If symptoms improve and immune-mediated etiology is ruled out, re-start avelumab therapy. If symptoms do not improve/worsen, viral myocarditis is excluded, and immune-mediated etiology is suspected or confirmed following cardiology consult, manage as immune-mediated myocarditis.

Immune-mediated myocarditis	Permanently discontinue avelumab. Guideline based supportive treatment as appropriate per cardiology consult.* Methylprednisolone 1-2 mg/kg/day.	Once improving, taper steroids over at least 1 month and add prophylactic antibiotics for opportunistic infections. If no improvement or worsening, consider additional immunosuppressions (e.g. azathioprine, cyclosporine A)
*Local guidelines, or eg. ESC or AHA guidelines ESC guidelines website: https://www.escardio.org/Guidelines/Clinical-Practice-Guidelines AHA guidelines website: http://professional.heart.org/professional/GuidelinesStatements/searchresults.jsp?q=&y=&t=1001		

5.6 Concomitant Medications

Concomitant medication will be evaluated at each study visit during study treatment. Concomitant medications include all vitamins, herbal remedies, over the counter, and prescription medications. Bone anti-resorptive therapy (denosumab, zoledronic acid) is permitted concurrently. ADT in the form of GnRH agonists or antagonists is permitted as part of the study as per standard of care practice. For patients on enzalutamide during screening, enzalutamide is permitted to be continued on study following progression per eligibility criteria. Enzalutamide will be able to be restarted during screening prior to study entry in patients who have had prior progression on enzalutamide per the discretion of the treating physician.

The following medications are prohibited within 2 weeks of enrollment and while on study drug, unless otherwise indicated below:

- Flutamide, bicalutamide or nilutamide;
- 5 α-reductase inhibitors (finasteride, dutasteride) are permitted concurrently;
- Estrogens;
- Abiraterone acetate
- Systemic glucocorticoids greater than the equivalent of 10 mg per day of prednisone unless required to treat an immune related ADR or needed as pre-treatment for an allergy to contrast;
- Androgens (testosterone, dihydroepiandrosterone [DHEA], etc.);
- All other investigational, chemotherapeutic, biologic, and radiopharmaceutical anti-cancer agents are prohibited within 4 weeks of enrollment and for the duration of study treatment
- Any herbal or complementary treatments that, in the opinion of the treating physician may increase the risk to the patient, are prohibited.

The following treatments do not require study discontinuation:

- Blood transfusions and growth factor support per standard of care and institutional guidelines;

- Steroids given at a maximum equivalent daily dose of 10 mg of prednisone;
- Pain therapy per standard of care and institutional guidelines

5.7 Study Drug Blinding

Not applicable, this is an open-label study

5.8 Randomization

Not applicable, this is a non-randomized study

5.9 Rationale for Selection of Dose, Regimen, and Treatment Duration

The dosing used for both the GnRH agonist and avelumab (10 mg/kg IV every 2 weeks) is derived from earlier studies described in Section 3.3.2.1.

5.10 Definition of Evaluable Subjects, On Study, and End of Study

Patients who consent but do not receive a dose of study drug will be replaced and will not be considered evaluable.

All subjects enrolled onto the study who receive at least one dose of avelumab will be included in the intention-to-treat analysis for the primary endpoint.

All subjects enrolled onto the study who receive at least one dose of avelumab will be evaluable for the secondary and exploratory endpoints.

Given the potential risk for delayed immune-related toxicities, safety follow-up must be performed 28 days after the last dose of avelumab administration.

The extended safety follow-up beyond 28 days after last study drug administration may be performed either via a site visit or via a telephone call with subsequent site visit requested in case any concerns noted during the telephone call.

5.11 Early Study Termination

This study can be terminated at any time for any reason by the PI-sponsor. If this occurs, all subjects on study will be notified as soon as possible. Additional procedures and/or follow up should occur in accordance with Section 8.8, which describes procedures and process for prematurely withdrawn subjects

6 STUDY DRUG

6.1 Names, Classification, and Mechanism of Action

Avelumab (MSB0010718C) is a fully human antibody of the immunoglobulin G (IgG) 1 isotype that

specifically targets and blocks PD-L1, the ligand for PD-1, thus removing the suppressive effects of PD-L1 on the anti-tumor $CD8^+$ T cells. Pfizer is developing avelumab for the treatment of cancer. Avelumab is FDA-approved for treatment of adults and pediatric patients 12 years and older with metastatic Merkel cell carcinoma in the United States.

6.2 Packaging and Labeling

Avelumab drug product is a sterile, clear, and colorless concentrate for solution intended for intravenous (IV) infusion. The drug is presented at a concentration of 20 mg/mL in single-use glass vial containing 200 mg of avelumab.

6.3 Supply, Receipt, and Storage

Avelumab drug product must be stored at 2°C to 8°C until use, and it must not be frozen. Rough shaking of avelumab product must be avoided. Avelumab drug product must be diluted with 0.9% saline solution; alternatively a 0.45% saline solution can be used if needed. It is recommended that the diluted avelumab solution is used immediately. For further data on avelumab please refer to the Investigator's Brochure.

It is given as an IV in an approved chemotherapy infusion center by certified chemotherapy nurses.

6.4 Special Precautions for Administration

Premedication: In order to mitigate infusion-related reactions, a premedication with an antihistamine and with paracetamol (acetaminophen) 30 to 60 minutes prior to each dose of avelumab is mandatory (for example, 25-50 mg diphenhydramine and 500-650 mg paracetamol IV or oral). This may be modified based on local treatment standards and guidelines, as appropriate. Subjects may also be pre-medicated with steroids and/or oral or inhaled cromolyn sodium at the discretion of the provider.

Setting: Avelumab should be administered in a setting that allows for immediate access to an intensive care unit or equivalent environment and administration of therapy for anaphylaxis, such as the ability to implement immediate resuscitation measures. Avelumab should be given over 2 hours (-10 min/+20min). Steroids (dexamethasone 10 mg), epinephrine (1:1,000 dilution), allergy medications (IV antihistamines), bronchodilators, or equivalents, and oxygen should be available for immediate access.

Observation period: Following avelumab infusions, subjects must be observed for 30 minutes post-infusion for potential infusion-related reactions.

7 SUBJECT ELIGIBILITY

7.1 Inclusion Criteria

1. Neuroendocrine-like prostate cancer, based on histology OR based on clinical presentation as defined by meeting one of the two below criteria. All subjects must submit their primary tumor or metastatic biopsy pathology specimens to the Duke Cancer Institute where they will be centrally reviewed by Duke Pathology (Dr. Jiaoti Huang). Central Duke pathologic review is not required for screening but rather for confirmation of histologic subtype. Local pathologic review is sufficient for eligibility determination.
    a. Criterion 1: Presence of 1 of 3 histologically proven diagnoses: **1)** Primary small cell carcinoma of the prostate, defined by classic histologic features such as small tumor cells with scanty cytoplasm, darkly stained nuclei with homogeneous chromatin pattern. The tumor cells do not form glandular structure but grow as solid sheets with frequent mitotic figures and necrosis; **2)** Intermediate atypical carcinoma of the prostate, which has histologic features distinct from small cell carcinoma or adenocarcinoma. The tumor grows as solid sheets or vague glandular structures. The tumor cells have moderate amounts of cytoplasm and centrally located, round and regular nuclei with fine, granular and homogeneous chromatin. Mitosis and necrosis are absent; **3)** mixed histology tumors of the prostate, containing both adenocarcinoma and neuroendocrine or small cell components.
    b. Criterion 2: Presence of histologically proven adenocarcinoma of the prostate without any sign of neuroendocrine or small cell histology that is radiographically progressing despite castrate levels of testosterone (<50 ng/mL) with the following poor risk features:
        i. Prior progression despite therapy with either abiraterone acetate and/or enzalutamide
        ii. At least one of the following: 1) Liver metastases; 2) Bulky radiographic progression (≥2 cm short axis lymph nodes or ≥1 cm long axis visceral metastases) combined with low serum PSA (<10ng/mL); 3) High serum LDH (>1X upper limit of normal).

2. Measurable disease as defined by modified PCWG3 using iRECIST criteria

3. Available tumor tissue for pathologic review and correlative studies. Tumor tissue (localized or metastatic) does not need to be received but rather identified and available (slides and/or blocks) to be sent to Duke.

4. Documented progressive metastatic CRPC based on at least one of the following criteria:

    a. PSA progression defined as 25% increase over baseline value with an increase in the absolute value of at least 2.0 ng/mL that is confirmed by another PSA level with a minimum of a 1 week interval and a minimum PSA of 2.0 ng/mL. Note: If confirmed rise is the only indication of progression, a minimal starting value of 1.0 ng/mL is acceptable, unless pure small-cell carcinoma.
    b. Soft-tissue progression based on new lesions or growth of existing soft tissue metastases.
    c. Progression of bone disease (evaluable disease) or (new bone lesion(s)) by bone scan.

5. Castrate levels of serum total testosterone (≤50 ng/dl) OR ongoing documented ADT unless pure small cell prostate cancer is present.

6. Previous use of radiation to metastatic site(s) at any time prior to enrollment is allowed, provided that this site is not the only measurable disease present or unless that solitary site is progressing following radiation.

7. Patients should have received at least one line of approved chemotherapy and/or hormonal therapy

8. Previous cytotoxic chemotherapy including cisplatin, carboplatin, oxaliplatin, etoposide, docetaxel, cabazitaxel, and gemcitabine is allowed, up to 3 prior regimens.

9. Karnofsky performance status of 70 or higher.

10. Acceptable initial laboratory values within 14 days of Cycle 1 Day 1 according to the below table:

ANC	≥ 1500/µl
Hemoglobin	≥ 9.0 g/dL(prior transfusion permitted)
Platelet count	≥ 100,000/µl
Creatinine	≤ 2.0 x the institutional upper limit of normal (ULN) OR creatinine clearance >30 ml/min
Potassium	≥ 3.5 mmol/L (within institutional normal range)
Bilirubin	≤ 1.5 x ULN (unless documented Gilbert's disease)
SGOT (AST)	≤ 2.5x ULN, or ≤5x ULN in patients with documented liver metastases
SGPT (ALT)	≤ 2.5x ULN or ≤5x ULN in patients with documented liver metastases

11. Age >18

12. Highly effective contraception for male subjects with childbearing potential throughout the study and for at least 60 days after last avelumab treatment administration if the risk of conception exists.

13. Willing and able to provide written informed consent and HIPAA authorization for the release of personal health information.

14. Life expectancy of over 3 months as determined by treating physician.

7.2 Exclusion Criteria

1. Prior usage of PD-1 inhibitors, programed-death ligand 1 and/or 2 inhibitors, CTLA-4 inhibitors including but not limited to ipilimumab, nivolumab, avelumab, durvalumab, tremelimumab, and pembrolizumab.

2. Active on-going immunologic or autoimmune disease including but not limited to systemic or cutaneous lupus erythematosus, cutaneous psoriasis, psoriatic arthritis, rheumatoid arthritis, scleroderma, sicca syndrome, polymyalgia rheumatica, polyarteritis nodosa, granulomatous

polyangiitis, microscopic polyangiitis, polyarteritis nodosa, temporal arteritis, giant cell arteritis, dermatomyositis, Kawasaki disease.

3. Previous malignancy within 3 years other than non-melanomatous skin cancers or cancers of low malignant potential such as non-invasive urothelial carcinoma.

4. Any other on-going chemotherapeutic, biologic, radiopharmaceutical, or investigational agent currently or within 28 days of Cycle 1 Day 1.

5. Prior use of abiraterone and other hormonal agents used to treat prostate cancer are permitted but abiraterone acetate should be stopped prior to study treatment initiation.

6. Current usage of immunosuppressant medication except for a) intranasal, inhaled, and topical corticosteroids and b) systemic corticosteroids equivalent to ≤ 10 mg/day of prednisone, c) steroids as premedication for hypersensitivity reactions (e.g. CT scan premedication).

7. Prior organ transplantation including allogeneic stem-cell transplants.

8. Active bacterial or viral infections requiring systemic therapy.

9. Current active infections with HIV/AIDS, Hepatitis B, and Hepatitis C requiring treatment.

10. Live virus vaccination within 4 weeks of the first dose of avelumab (inactivated vaccines are allowed).

11. Known prior hypersensitivity to the investigational product or any component formulations, including known severe hypersensitivity reactions to monoclonal antibodies.

12. Clinically significant (i.e. active) cardiovascular disease: cerebral vascular accident (<6 months prior to enrollment), myocardial infarction (<6 months prior to enrollment), unstable angina, congestive heart failure (≥ New York Heart Association Classification Class II), or serious cardiac arrhythmia requiring medication.

13. Persisting toxicity related to prior therapy (NCI CTCAE v. 4.03 Grade > 1); however, alopecia, sensory neuropathy Grade ≤ 2, Grade 2 anemia, or other Grade ≤ 2 not constituting a safety risk based on investigator's judgment are acceptable.

14. Other severe acute or chronic medical conditions including colitis, inflammatory bowel disease, pneumonitis, pulmonary fibrosis or psychiatric conditions including recent (within the past year) or active suicidal ideation or behavior; or laboratory abnormalities that may increase the risk associated with study participation or study treatment administration or may interfere with the interpretation of study results and, in the judgment of the investigator, would make the patient inappropriate for entry into this study.

8 SCREENING AND ON-STUDY TESTS AND PROCEDURES

	≤35 Days Prior to Dosing	Cycle Duration = 28 days (+/- 3 day window of allowance) [2]		Post Treatment (+/- 7 days)		
Activity	**Screening / baseline**	**Day 1 of every cycle[1, 2, 10, 16, 17]**	**Day 15 of every cycle[2]**	**EOT / Progression/ Withdrawal[3]**	**Safety follow up (28 days post treatment)**	**Long Term Follow-Up (every 3 months)**
Baseline Documentation						
Informed Consent	X					
Inclusion/Exclusion Criteria	X					
Central histology review of tumor tissue, Duke pathology	X					
Medical/Oncological History[4]	X	X	X	X	X	X
Laboratory Studies						
Hematology[5]	X	X	X	X	X	
Blood Chemistry[5]	X	X	X	X	X	
Urinalysis[6]	X					
PSA	X	X		X	X	
Testosterone	X	X		X		
Thyroid Studies[5]	X	X		X	X	
Tumor Markers[7]	X	X		X		
Study Treatment						
Study Treatment – ADT +/- enzalutamide (SOC)[8]	X	X	X	X		
Study Treatment – Avelumab[9]		X	X			
Tumor Assessments						
Tumor Imaging[10]	X	X		X		
Post-Progression Biopsy[11]				X		
Clinical Assessments						
Physical Examination[12]	X	X	X	X	X	

KPS, Weight, Vitals	X	X	X	X	X	
Adverse Events[13]		X	X	X	X	
Conmed/Treatment[14]	X	X	X	X	X	
Survival Follow-up[15]						X
Research Laboratory Studies (Cycle 1 day 1, Cycle 3 day 1 and EOT)[3]						
Immune cell monitoring[16]		X		X		
Cell Free DNA[16]		X		X		
CTCs for culture [17]		X		X		
Patient Reported Outcomes						
FACT-P[18]		X		X		

Footnotes:

1. **Day 1 Cycle 1 Assessments:** Hematology, blood chemistry, PSA, testosterone, and PSA need **not** be obtained on day 1 if a screening sample has been performed within 14 days. Baseline Signs/symptoms are only needed on Cycle 1 Day 1. Thyroid studies do not need to be repeated on Day 1 of Cycle 1 if obtained within the screening window.
2. **Cycle 1 Day 15+:** Avelumab can be given up to 3 days before or after the expected start date of each infusion/treatment day after Cycle 1 Day 1. Cycles are continued until progression or until significant adverse event.
3. **End of Treatment/Progression/Withdrawal: To occur at time of decision to end treatment.** These assessments do **not** need to be completed if they have been performed within 7 days of study withdrawal (within the last 6 weeks for tumor assessments). +/- 7 day window of allowance. Treatment beyond radiologic or PSA progression is permitted if there is potential for clinical benefit with continued therapy. Research blood samples will be collected at iRECIST-defined progression or at the EOT visit, whichever comes first.
4. **Medical/Oncological History:** Includes oncologic history, demographics, history of other disease processes and concomitant illnesses. Central review of pathology at Duke is required at baseline.
5. **Samples for hematology, blood chemistry, and thyroid studies**: CBC w/ differential, CMP (including AST, ALT, Alkaline Phosphatase), LDH, phosphorus, TSH, free T4. Thyroid studies must be performed at least every 8 weeks starting after cycle 1 and at end of treatment/safety follow-up (if not performed in the previous 8 weeks). PSA and testosterone should be performed at least every 4 weeks.
6. **Urinalysis:** Tests will be done at screening, then as clinically indicated thereafter; tests to be performed at the local laboratory. Urinalysis should also include a urine spot protein at baseline. A 24 hour urine analysis is required if urine protein is > 1+.
7. **Tumor Markers:** CEA and chromogranin A will be measured at baseline and those that are elevated will be measured every 4 weeks thereafter. (Standard of care)
8. **Standard of Care Treatment (Androgen Deprivation Therapy (ADT), +/- enzalutamide)**: Patients already on ADT at study entry should continue with dosing and administration is to be determined by the treating provider but can include gonadotropin releasing hormone

agonists or antagonists. ADT will continue throughout all cycles. If patient has pure SCPC they do not need to be started on ADT but are allowed to continue per treating provider if already on ADT. Concurrent enzalutamide is permitted.

9. **Study Treatment (Avelumab)**: Avelumab will be administered at 10 mg/kg IV every 2 weeks. One cycle is 2 infusions (4 weeks).
10. **Tumor imaging:** Bone scan, and either CT or MRI scans of the chest, abdomen, and pelvis will be performed to assess disease status at baseline as well as every 8 weeks or at treatment discontinuation (if imaging did not occur within 6 weeks of visit) as well as whenever disease progression is suspected, to confirm partial or complete response. NaF-PET/CT may be used in place of bone scan and CT in select cases. In all cases, the same imaging modality should be used throughout the study on individual subjects. Baseline tumor imaging must be performed within 35 days of cycle 1 day 1. MRI brain should be done in all subjects at baseline if indicated clinically and should be followed every 8 weeks with the other scans if metastasis(es) are found or if disease progression is suspected. Allowable window for tumor assessment imaging studies is +/- 7 days. Subjects removed from therapy for any reason other than disease progression will continue to be followed for radiographic progression until additional treatments are started, when available.
11. **Post-Progression Biopsy:** An optional standard of care post-treatment progression biopsy will also be collected and additional tissue for research will be banked in the Biospecimen Repository & Processing Core (BRPC) under Pro00080869 for future research on resistance mechanisms including assessment of immune checkpoint status.
12. **Physical Examination:** Examination of major body systems. It does **not** need to be done cycle 1, day 1 if performed within the last 7 days.
13. **Adverse Events:** Subjects must be followed for adverse events from the first day of study treatment until 28 days after the last dose of study treatment, or until all serious or study drug-related toxicities have resolved or are determined to be "chronic" or "stable", whichever is earlier. Serious adverse events should be monitored and reported from the time the patient starts study drug treatment as described in the protocol.
14. **Concomitant medications/treatments:** Concomitant medications and treatments will be recorded from up to 35 days prior to the start of study treatment, during the study, and through the safety follow up visit.
15. **Survival Follow up:** After the EOT/Withdrawal of treatment, subjects will be surveyed for their survival status by either a direct phone call or through the chart review. A clinic visit on study is not needed. The subjects will be surveyed every 3 months for up to 3 years, unless the subject has requested otherwise.
16. **Immune Cell Monitoring and Cell Free DNA:** Research blood samples will be collected at 3 time points during the course of therapy. At initiation (Cycle 1 Day 1), on Cycle 3 Day 1, and at progression. A total of four blood tubes will be collected at each interval. Three tubes will be processed for the immune cells. Plasma samples (single EDTA tube) will also be collected and processed at each time point. (see laboratory manual for details on shipping and handling)
17. **CTCs for culture:** Research blood will be collected on cycle 1 day 1 and at progression for circulating tumor cell enrichment and cell culture.
18. **PROs:** Patient reported outcomes will be assessed using the Functional Assessment of Cancer Therapy – Prostate (FACT-P). Subjects will first complete the questionnaire in clinic prior to administration of study medication. Subjects will then be asked to complete a follow up FACT-P on day 1 of cycles 1, 4, 7 and every 3 subsequent cycles, and at End of Treatment/Withdrawal

8.1 Screening Examination

The screening examination will take place within 35 days of initiation of therapy. An informed consent form must be signed by the subject before any screening procedure takes place.

Subject data to be collected at the Screening Examination includes:

- Informed consent process utilizing a signed and dated IRB-approved ICF
- Confirmation of inclusion/exclusion criteria
- Medical history including demographics, concomitant illnesses and oncologic history. Oncologic history must include specific documentation of prostate cancer histologic diagnosis.
- Prior and concomitant medications and non-pharmacologic treatments taken within 4 weeks of screening will be recorded. In addition, all prior treatments including surgery and radiotherapy for prostate cancer will be recorded, regardless of when administered.
- Standard of Care tumor imaging within 35 days of Cycle 1, Day 1 must include:
    - CT of the chest, abdomen, and pelvis for tumor assessment And
    - Whole body bone scan (99-Technetium), standard-of-care
    - Note: NaF-PET/CT may be used in place of bone scan and CT in select cases
    - MRI Brain should be performed if clinically indicated based on symptoms of CNS metastases
- Sample collection for the following laboratory evaluations (all standard-of-care):
    - Complete blood count (CBC) with differential: WBC count with differential, platelet count, hemoglobin, and hematocrit.
    - Serum chemistries: Sodium, potassium, chloride, blood urea nitrogen (BUN) or urea, creatinine, glucose, carbon dioxide (CO_2) or bicarbonate, calcium, total protein, aspartate aminotransferase (AST), alanine aminotransferase (ALT), albumin, total bilirubin, and alkaline phosphatase, thyroid stimulating hormone (TSH), free thyroxine (fT4).
    - Urinalysis
    - Testosterone
    - PSA levels.
    - Tumor markers (CEA and chromogranin A)
- Physical examination to be conducted and height (cm), weight (kg), and vital signs (including temperature [°C], blood pressure [mmHg], heart rate [beats per minute], and respiratory rate [breaths per minute]) to be measured and recorded
- Karnofsky performance status
- Pathology review

8.2 Subject Registration and Enrollment

8.2.1 Informed Consent

Authorized study personnel should fully explain the scope of the study to each subject before obtaining informed consent. Consent should occur prior to any research procedures and before formal screening procedures. Subjects should be advised of any known risks inherent in the planned

procedures, of any alternative treatment options, of their right to withdraw from the study at any time for any reason, and of their right to privacy.

When obtaining informed consent, study personnel should:
First: Confirm that the subject is a potential candidate for study participation.
Next: Obtain dated and signed informed consent.
Finally: Confirm that the subject is eligible as defined in Section 7.0 (Inclusion/Exclusion Criteria). A record of subjects who fail to meet entry criteria (i.e., screening failures) will be maintained.

Subjects will be entered into the Duke clinical trial subject registry per institutional policy.

8.2.2 Registration

Subject registration at each study site/institution will be conducted according to the institution's established policies and all sites will be overseen by the Duke University Medical Center Genitourinary Oncology Group. Prior to registration, subjects will be asked to sign and date an Institutional Review Board (IRB)-approved consent form. After obtaining informed consent, the consent document and any registration documents will be submitted for review and registration of the subject by the lead site (Duke). All consented subjects will be registered and assigned a unique study ID. A record of subjects who fail to meet entry criteria (i.e., screen failures) will be maintained.

Refer to Subject Registration Instructions in the Coordinator Manual for details.

8.2.3 Enrollment

Subjects will be enrolled only after all pre-treatment screening evaluations are completed and all eligibility criteria are met. Once the subject has been registered and found to meet all eligibility criteria, the subject will be approved for enrollment. Study treatment must not commence until the subject has received his/her identification number and enrollment approval from the lead site.

8.3 Run-In Period

Not applicable

8.4 Treatment Period

Treatment will be administered on an outpatient basis. Avelumab will be given every 2 weeks according to the calendar of events. On study procedures are detailed in the schedule of events including blood tests, imaging, medical history and concomitant medications, toxicity assessments, FACT-P assessments, and correlative biomarkers.

8.5 End of Treatment

In the event of disease progression, unacceptable toxicity, or withdrawal of consent, study treatment is to be stopped and an end-of-treatment visit is to be conducted within 7 days.
The following procedures are to be conducted at the end-of-treatment visit:

- Concomitant medications and non-pharmacologic treatments to be reviewed and recorded.
- Sample collection for the following laboratory evaluations (all standard-of-care):

- CBC: WBC with differential, platelet count, hemoglobin, and hematocrit.
- Chemistries: sodium, potassium, chloride, blood urea nitrogen (BUN) or urea, creatinine, glucose, carbon dioxide (CO_2) or bicarbonate, calcium, total protein, aspartate aminotransferase (AST), alanine aminotransferase (ALT), albumin, total bilirubin, and alkaline phosphatase, thyroid stimulating hormone (TSH), free thyroxine (fT4).
- Testosterone
- PSA
- Tumor markers (CEA and chromogranin A)
- Progression biopsy of metastatic site (optional) and research blood samples (see laboratory manual).

- Research blood sample collection will occur at this visit or iRECIST defined progression, whichever comes first
- Tumor imaging as per standard of care practices to document progression
- Physical examination to be conducted, including weight (kg) and vital signs (including temperature [°C], blood pressure [mmHg], heart rate [beats per minute], and respiratory rate [breaths per minute]).
- Karnofsky performance status.
- Functional Assessment of Cancer Therapy – Prostate (FACT-P) will be administered

8.6 Follow up period

8.6.1 Safety Follow-up visit

The safety follow-up visit is to occur 28 days (+/- 7 days) after the last dose of study agent. Subjects that discontinue treatment due to reasons other than progressive disease will be followed until progression through Standard of Care scans.

8.6.2 Extended safety follow-up

Given the potential risk for delayed immune-related toxicities, extended safety follow-up must be performed up to 90 days after the last dose of avelumab administration for all serious or study drug-related toxicities were not resolved or not determined to be “chronic” or “stable” within 28 days after the last dose of avelumab. The extended safety follow-up beyond 28 days after last study drug administration may be performed either via a site visit or via a telephone call with subsequent site visit requested in case any concerns noted during the telephone call.

8.6.3 Survival Follow-up Period

Subjects will be followed for disease progression and death for a maximum period of 3 years from the date that the Subjects were enrolled to the protocol. Imaging studies and clinical visits will be performed as per standard-of-care.

8.7 End of Study

After progression or withdrawal from treatment, each subject will be followed every 3 months following their end-of-treatment visit for a total of 3 years from study enrollment for survival follow

up. The overall end of study will occur when the last enrolled subject has completed his 3 year follow-up visit or death.

8.8 Early Withdrawal of Subjects(s)

8.8.1 Criteria for Early Withdrawal

Subjects may voluntarily withdraw from the study at any time. The PI may also withdraw a subject from the study at any time based on his/her discretion.

Reasons for PI-initiated withdrawal may include the following:

- Symptomatic disease progression or objective radiologic progression that is not consistent with iRECIST
- Unacceptable toxicity, intercurrent illness, or changes in the patient's condition (at the discretion of the treating physician) — Reason(s) for removal must be clearly documented in the physician progress note
- The patient may withdraw from study treatment at any time for any reason and still be followed per protocol**.**
- Provider decision that the subject is no longer clinically benefiting from avelumab

8.8.2 Follow-up Requirements for Early Withdrawal

Upon early withdrawal from study treatment, an end of treatment visit should be conducted within 7 days as described above. At withdrawal, all on-going study-related toxicities and SAEs should be followed until resolution, unless in the investigator's opinion, the condition is unlikely to resolve due to the subject's underlying disease. Subjects should be followed up for new AEs for 90 calendar days after the last dose of avelumab. All new AEs possibly related to study treatment occurring during that period should be collected.

8.8.3 Replacement of Early Withdrawal(s)

Patients who consent but do not receive a dose of study drug will be replaced and will not be considered evaluable. Subjects who prematurely withdraw but received a dose of study drug will not be replaced.

8.9 Study Assessments and Definitions

8.9.1 Medical History

At the initial visit, the detailed medical history will include concomitant illnesses and oncologic history. All prior treatments including surgery, chemotherapy, hormonal therapy, and radiotherapy for prostate cancer will be recorded, regardless of when administered. This medical history will be

updated at subsequent visits. Concomitant medications and non-pharmacologic treatments taken will be recorded at each visit.

8.9.2 Physical Exam

Physical examination should include: height (cm – screening visit only), weight (kg), physical exam findings, and vital signs. Vital signs include temperature [°C], blood pressure [mmHg], heart rate [beats per minute], and respiratory rate [breaths per minute]. Karnofsky performance status will be assessed and recorded at each visit. All additional elements of the physical exam will be documented per the provider's discretion.

8.9.3 Correlative Exploratory Biomarker Studies

1. To describe the impact of PD-L1 inhibition with avelumab on blood-based biomarker changes over time, including PSA, chromogranin-A, cell free DNA, LDH, and alkaline phosphatase. For Objective 1, Subjects will have standard of care serum CEA and chromogranin A, LDH, PSA, and alkaline phosphatase drawn per the protocol. Samples will be drawn on Day 1 of every cycle. Cell free tumor DNA from plasma (research) will be collected and analyzed at baseline, cycle 3 day 1, and at progression. Changes in these biomarkers over time will be described using descriptive statistics only without formal testing. Please see the lab manual for associated details. Given that these are standard of care measures for NEPC patients and may be clinically useful in monitoring response to treatment, these are not considered research tests.

2. To determine if levels of circulating biomarkers secreted by neuroendocrine-like prostate cancers correlate with clinical and radiographic treatment response. For this objective, baseline and longitudinal levels of the biomarkers described in objective 1 will be associated with radiographic and clinical response to avelumab as well as duration of response, PFS, and survival. These are considered exploratory analyses.

3. To determine if the presence of different immunohistochemical markers on the pre-treatment biopsy specimens prognosticates clinical and radiographic treatment response. For Objective 3, all Subjects will have already submitted a sample of tumor tissue for central review at Duke University Department of Pathology. Acceptable tissues include local prostate biopsies, surgical specimens, or metastatic biopsies. Outside slides or recuts of outside tissue is required for histologic review prior to enrollment as part of the screening process. Additional formalin fixed tissue (block, biopsy, or slides) may be kept for biomarker studies specific to this trial. These samples will then be assessed for immune checkpoint biomarker expression (PD-1, PD-L1, CD8, and CTLA4 among others) as well as other expression of other tumor specific proteins (PD-L1, PD-L2, AR, PSA, FOXA2, p53, Rb, Cyclin D1, Chromogranin A, synaptophysin, p38 activity, SNAIL, among others). Associations of pre-treatment biopsies with primary and secondary outcomes will be described in an exploratory fashion.

For subjects that opt-in for the post-progression biopsy, additional tissue will also be collected and banked in the Biospecimen Repository & Processing Core (BRPC) under Pro00080869 for future research to identify resistance mechanisms and immune checkpoint status.

4. To determine if the level of different circulating immune cells correlate with both progressive addition of immunotherapy as well as clinical and radiographic treatment response or disease progression. For Objective 4, peripheral blood for immune subset phenotyping will be collected from subjects at baseline (Cycle 1 Day 1), at Cycle 3 Day 1, and at disease progression. These will then be processed by the Duke Substrate Services Core & Research Support (SSCRS) laboratory and analyzed in the Duke Immune Profiling Core Laboratory (DIPC) (Kent Weinhold) at Duke University. Changes in immune cell phenotypes over time will be described during avelumab therapy, as will associations with clinical/radiographic responses and duration of response, PFS. Please see the lab manual for specific details about tube types, processing, collection and storage.

5. To determine if levels of cell free DNA correlate with clinical and radiographic treatment response. For objective 5, peripheral blood and plasma will be drawn to collect cell free DNA for analysis. We will measure and characterize cell free DNA at baseline (Cycle 1 Day 1), at Cycle 3 Day 1, and at disease progression. Cell free DNA will be analyzed using whole exome sequencing. Please see the lab manual for further details of plasma processing and collection/storage.

6. To isolate prostate neuroendocrine-like CTCs for ex vivo culture and characterization studies. One 7.5 mL EDTA tube of research blood will be collected on cycle 1 day 1 and at progression for circulating tumor cell enrichment, cell culture and serial passaging ex vivo as cell lines for characterization and long-term studies of prostate cancer biology. Please see the lab manual for further details of collection and processing samples for CTCs.

8.9.4 Imaging Assessments

All baseline evaluations will be performed as closely as possible to the beginning of treatment ($\leq$35 days). For subsequent evaluations, the method of assessment and techniques will be the same as those used at baseline.

To assess the antitumor effect of a treatment, imaging-based evaluation is preferable to evaluation by clinical examination. CT and MRI should be performed using contiguous slices of 10 mm or less. Spiral CT should be performed using a 5-mm contiguous reconstruction algorithm (interval). If a 5-mm contiguous reconstruction algorithm (interval) is not used, as a general rule, the lesion diameter should be no less than double the reconstruction algorithm (interval) and must be at least 20 mm for nonspiral CT or at least 10 mm for spiral CT. (If available, spiral CT is preferred in all instances.) This applies to tumors of the chest, abdomen, and pelvis. Head and neck tumors and those of the extremities typically require specific protocols. Sodium Fluoride PET-CT +/- IV contrast may be used as an alternative to CT/bone scan if available. Brain MRI should be ordered as per standard of care practice in symptomatic or small cell carcinoma patients.

8.9.5 PSA

PSA testing should be performed at each cycle (every 4 weeks). To report PSA-based outcomes, PCWG3 recommends that the percent of change in PSA from baseline to 8 and 12 weeks depending on trial design (or earlier for those who discontinue therapy) and the maximum decline in PSA that occurs at any point after treatment be reported for each patient using a waterfall plot.

8.9.6 Non-PSA Tumor markers (Standard of care)

Chromogranin-A levels will be measured at baseline and on day 1 of each cycle if elevated. CEA should be assessed at baseline and if elevated, followed on day 1 of each cycle.

8.9.7 Measurable disease

According to iRECIST[32], measurable disease is defined as at least 1 lesion ≥ 10 mm in its longest diameter as measured with computerized tomography (CT) with slice thickness no greater than 5 mm; ≥ 10 mm as measured with calipers on clinical exam; or >15 mm for nodal metastases using the shortest diameter. All tumor measurements will be taken using a ruler or calipers and recorded in millimeters (or decimal fractions of centimeters). In the case of skin lesions, documentation by color photography, including a ruler to estimate the size of the lesion, is recommended.

Only tumor lesions that have not been previously irradiated will be considered measurable.

8.9.8 Nonmeasurable disease

Following iRECIST, all other lesions (or sites of disease) will be considered nonmeasurable disease. This includes small lesions (longest diameter < 20 mm with conventional techniques or < 10 mm using spiral CT scan) and any of the following:

- bone lesions
- ascites
- pleural or pericardial effusion
- lymphangitis cutis or pulmonis
- abdominal masses that are not confirmed and followed by imaging techniques
- cystic lesions
- lesions occurring within a previously irradiated area unless they are documented as new lesions since the completion of radiation therapy

8.9.9 Target (nodal and visceral) lesions

Following iRECIST, progression in a nodal or visceral site (i.e., liver and lung) is sufficient to document disease progression. The presence or absence of nodal and visceral disease before and after treatment should be recorded separately.

All measurable lesions (up to a maximum of 5 lesions per organ and 10 lesions in total) will be identified as target lesions to be measured and recorded at baseline. The target lesions should be representative of all involved organs. Target lesions will be selected on the basis of size (i.e., the largest area) and suitability for accurate, repeated measurements (either by imaging techniques or clinically). The sum of the longest diameter (LD) of all target lesions will be calculated and reported as the baseline sum LD. The baseline sum LD will be used as a reference by which to characterize the objective tumor response.

Because small lymph nodes are difficult to measure accurately and may not be malignant, a lymph node must measure at least 1.5 cm by short axis by spiral CT to be considered a target lesion.[30]

8.9.10 Bone lesions

When the bone scan is the sole indicator of progression at baseline, disease progression in bone is defined as 2 or more new lesions seen on bone scan compared with a prior scan used for trial entry.[30] In situations where scan findings suggest a flare reaction or where new lesion(s) may represent trauma, confirm these results with other imaging modalities (e.g., MRI or fine-cut CT). If many new areas of uptake are observed, confirmation is generally not necessary.

8.9.11 Nontarget lesions

All other lesions (or sites of disease) will be identified as nontarget lesions and recorded at baseline. Nontarget lesions will include measurable lesions that exceed the maximum number per organ (5) or total of all involved organs (10), as well as nonmeasurable lesions. The presence or absence of these lesions will be recorded on the CRF and should be evaluated at the same assessment time points as all target lesions.

8.9.12 New lesions

The appearance of up to 10 new measurable lesions should be recorded. Each new lesion should be reassessed using the same imaging modality at each time point. If measurable, the LD of each new lesion (including lymph nodes) should be recorded in the CRF and the sum LD of new and old lesions should be calculated. See Table 1 for a description of the determination of progression based on the presence of new lesions.

Note: The appearance of a new lesion does not by itself satisfy the criteria for confirmed progressive disease. Rather, the tumor burden imposed by the new lesions must be evaluated within the context of the total tumor burden (i.e., preexisting plus new lesions). Confirming progression in target lesions, nontarget (i.e., other than bone) lesions, and bone lesions requires 2 assessment time points. The first must occur at Week 8 (or later) and the second occurring at least 6 weeks after the first. Progression declared at the first time point remains unconfirmed unless assessments at the second time point demonstrate continuing or worsening progression as described in section 8.10.

8.10 Response Criteria

Response and progression will be evaluated in this study using a modified PCWG3 where RECIST 1.1 is replaced with iRECIST[31] criteria and the guidelines for prostate cancer endpoints developed by the Prostate Cancer Clinical Trials Working Group (PCWG3).[30] In brief, iRECIST defines an immune unconfirmed progressive disease (UPD) on the basis of RECIST 1.1 principles and now requires confirmation of progression. Confirmation is done by observing either a further increase in size or number of new lesions identified (target, non-target) or progression by RECIST 1.1. However if progression is not confirmed but instead shrinkage occurs, compared to baseline, which meets RECIST 1.1 criteria of complete response, partial response, or stable disease; then the bar is reset so that UPD needs to occur again, compared with nadir values, and then be confirmed again.

Trial objectives are defined based on controlling, relieving, or eliminating disease manifestations that are present when treatment is initiated, or preventing or delaying the development of disease manifestations that are expected to occur (or in some cases both). Traditional measures of response reflect when a treatment is working and measures of progression indicate when a drug should be stopped. Because assessing response in bone (the most common site of prostate cancer spread) is uncertain and the clinical significance of PSA changes in response to therapy is not a reliable predictor of response, measures of response have been expanded in consortium trials to include measures of progression.

Subjects will need to be reevaluated for response every 2 cycles (or more frequently if indicated), according to the guidelines below.

8.10.1 Measurable soft-tissue lesions

When evaluating soft-tissue lesions, the definitions in Table 1 apply.

Table 1. RECIST 1.1 response criteria for target (soft-tissue) lesions

Response	Evaluation of Soft-Tissue Lesions
Complete response (CR)	the disappearance of clinical and radiological evidence of all target lesions and normalization of tumor marker levels
Partial response (PR)	a decrease from baseline ≥ 30% in the sum of the LD of all target lesions
Progressive disease (PD)	an increase ≥ 20% in the sum of the LD of all target lesions based on the smallest sum LD since treatment started or the appearance of one or more new lesions or the appearance of new lesions
Stable disease (SD)	neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD based on the smallest sum LD recorded since treatment started

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

8.10.2 PSA

As long as patient safety is the primary concern, in the absence of other indicators of disease progression, therapy should not be discontinued solely on the basis of a rise in PSA.
PSA progression is defined as the date that a 25% or greater increase and an absolute increase of 2.0 ng/mL or more from the nadir is documented and confirmed by a second value obtained 3 or more weeks later. Where no decline from baseline is documented, PSA progression is defined as a 25% increase from the baseline value along with an increase in absolute value of 2.0 ng/mL or more after 8 weeks.

8.10.3 Bone

Record post-treatment changes as either “no new lesions” or “new lesions.”

In the absence of clearly worsening soft-tissue (nodal and visceral) disease or disease-related symptoms, progression at the first scheduled assessment should be confirmed on a second scan performed 6 or more weeks later. In the rare case where visible lesions disappear, this too should be confirmed.

Progressing disease on bone scan is considered when at least 2 new lesions are observed. Yet, progression remains unconfirmed unless at least 2 *additional* new lesions appear at a subsequent time point.

Unless clinically indicated, there is no need to perform a follow-up bone scan before 12 weeks of treatment. To define disease progression requires a confirmatory scan (which shows additional new lesions compared with the first follow-up scan) performed 6 or more weeks later. When further progression is documented on the confirmatory scan, the date of progression recorded for the trial is the date of the first scan that shows the change.

8.10.4 Nontarget lesions

When assessing nontarget lesions, the definitions in Table 2 will apply. The overall assessment of preexisting plus new lesions at the first time point must show unequivocal progression. Progression at the first time point remains unconfirmed unless progression is confirmed to the same or greater extent at a subsequent time point.

Table 2. RECIST response criteria for nontarget lesions

Response	Evaluation of Nontarget Lesions
Complete response (CR)	the disappearance of all nontarget lesions and normalization of tumor marker levels
Incomplete response/ stable disease (SD)	the persistence of one or more nontarget lesions and/or maintenance of tumor marker levels above the normal limits
Progressive disease (PD)	the appearance of one or more new lesions and/or unequivocal progression of existing nontarget lesions

8.10.5 Patient-reported outcomes

FACT-P scores will be collected and described over time for this study to assess quality of life changes. No formal statistics will be applied to this exploratory endpoint.

Transient increases in pain may occur before improvement, and those occurring in the first 12 weeks should not affect the course of treatment in the absence of other compelling evidence of disease progression. Changes in symptoms should be confirmed as for other outcome measures. Monitor other domains that may help determine whether the disease is progressing, including worsening in global quality of life, developing urinary or bowel compromise, or needing to change anticancer therapy.

8.10.6 Evaluating best overall response

The best overall response is the best response recorded from the start of treatment until either disease progression or recurrence. The investigator's determination of best overall response will be based both on response criteria and on confirmation criteria. To be assigned a status of confirmed partial response or complete response, changes in tumor measurements must be confirmed by repeat assessment performed at least 4 weeks after the criteria for response are first met. To confirm stable disease, follow-up measurements must meet SD criteria at a minimum interval of 4 weeks after SD was first documented. Table 3 can be used as an assessment tool.

Note: If unconfirmed progression noted at the first time point is not confirmed at a second time point, the next assessment time point after the first that meets the criteria for progression will be treated as time point 1.

Table 3. Assessing Overall Response

Target Lesions	Nontarget Lesions	New Lesions	Overall Response
CR	CR	No	CR
CR	Incomplete response/SD	No	PR
PR	Non-PD	No	PR
SD	Non-PD	No	SD
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD

Abbreviations: CR, complete response; PD, progressive disease; PR, partial response; SD, stable disease.

Subjects with global deterioration of health status who require treatment to be discontinued without objective evidence of disease progression should be classified as having symptomatic deterioration. Every effort should be made to document their objective progression, even after discontinuing treatment.

Subjects who do not have tumor response assessment due to rapid progression or toxicity will be considered nonresponders, will be included in the denominator for the response rate, and will be classified into one of the categories listed below:

- death attributed to disease progression
- early discontinuation attributed to disease progression
- death attributed to drug toxicity
- early discontinuation attributed to drug toxicity

Note: If a subject receives subsequent therapy before tumor progression is documented, the reason for changing therapy must be reported. Reasons include clinical progression, drug toxicity, or secondary therapy for maintaining tumor response.

For immunotherapies, atypical patterns of response, including delayed responses, new lesions with mixed patterns of response, pseudoprogression due to immune infiltration (transient), and prolonged stable or partially responsive disease. In this study, we will describe the immune-

modified responses using the following **table 4**[40] PCWG3-modified RECIST 1.1 and immune-modified response and progression will be reported separately in this study.

Derivation of overall immune-related response for all assessed time points

Measurable response	Nonmeasurable response		Overall response
Index and new measurable lesions (total measurable tumor burden)†	Non-index lesions	New nonmeasurable lesions	Using irRC
100% decrease	Absent	Absent	irCR‡
≥50% decrease	Any	Any	irPR‡
<50% decrease to <25% increase	Any	Any	irSD
≥25% increase	Any	Any	irPD‡

* After Wolchok et al. (43). irCR = immune-related compete response—complete disappearance of all index and new measurable lesions; irPR = immune-related partial response—decrease in tumor volume ≥50% relative to baseline; irSD = immune-related stable disease—not meeting criteria for irCR or irPR, in absence of irPD; irPD = immune-related progressive disease—increase in tumor volume ≥25% relative to nadir.

† Index and non-index lesions are selected at baseline. Index lesions are measurable (>5 × 5 mm), and non-index lesions are not measurable (<5 × 5 mm, ascites, bone lesions, etc.). Changes are assessed relative to baseline and include measurable lesions only (>5 × 5 mm).

‡ Assuming response and progression are confirmed by a second assessment at least 4 weeks apart.

Table 4. Immune modified RECIST criteria.

8.11 Confirmatory Measures/Duration of Response

8.11.1 Confirming time-to-event outcomes

Any post-treatment change in disease status (imaging, biomarker studies), be it favorable or unfavorable, should be confirmed using a second assessment at a later time point 4 or more weeks later. Unconfirmed results will be reported as such.

8.11.2 Duration of overall response

Duration of overall response is measured from the time when partial response or complete response is first noted until the date when recurrent or progressive disease is objectively documented. Duration of overall complete response is measured from the time the criteria for complete response are first met until the first date that recurrent disease is objectively documented. Duration of stable disease is measured from the start of treatment until the criteria for progression are met.

8.11.3 Progression-free survival

Progression-free survival (PFS) is a composite endpoint defined as the time from study entry or random assignment to radiographic disease progression in bone or soft-tissue, symptoms (clinical deterioration), or death. PSA changes will not be used to define PFS in this study. A PFS estimate using both conventional PCWG3-modified RECIST 1.1 criteria and immune-modified RECIST criteria (**Table 4**) will be reported. Use an interval-censored approach in which all assessments of the composite PFS endpoint (i.e.bone, CT scans, and symptom assessments) are performed at the same time points. All assessments of disease should be collected at the same time interval every 8 weeks.

8.11.4 Response review

All subjects who meet eligibility criteria and receive at least 1 dose of study medication/undergo 1 scan or procedure will be included in the main analysis of the response rate, even if there are major protocol deviations (e.g., incorrect treatment schedule or drug administration). Each subject will be assigned to one of the following categories:

Table 5. Categories for Response to Treatment

Category	Response
1	Complete response
2	Partial response
3	Stable disease
4	Progressive disease
5	Early death from malignant disease
6	Early death from toxicity
7	Early death from other causes

9	Unknown (not assessable/insufficient data)

NOTE: By arbitrary convention, category 9 designates unknown status in a clinical database. Subjects in response categories 4 to 9 will be considered to have treatment failure (disease progression).

Conclusions are to be based on the population of all eligible subjects. Subanalyses may be performed on various subsets of subjects, such as those with no major protocol deviations or those who continued in the study for the entire treatment period (i.e., did not withdraw prematurely). Subanalyses will not serve as the basis for drawing conclusions concerning treatment efficacy.

9 SAFETY MONITORING AND REPORTING

The PI is responsible for the identification and documentation of adverse events and serious adverse events, as defined below. At each study visit, the PI or designee must assess, through non-suggestive inquiries of the subject or evaluation of study assessments, whether an AE or SAE has occurred.

9.1 Adverse Events

An adverse event (AE) is defined as any untoward medical occurrence in a subject administered a study drug and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a study drug, whether or not related to the study drug.

An abnormality identified during a medical test (e.g., laboratory parameter, vital sign, ECG data, physical exam) should be defined as an AE only if the abnormality meets one of the following criteria:

- Induces clinical signs or symptoms.
- Requires active intervention.
- Requires interruption or discontinuation of study medication.
- The abnormality or investigational value is clinically significant in the opinion of the investigator.

All adverse events, whether or not related to the study drug, must be fully and completely documented.

From the first dose of avelumab until 28 days after the last dose of avelumab, or until all serious or study drug-related toxicities have resolved or are determined to be “chronic” or “stable”, whichever is earlier, all AEs must be recorded in the subject medical record and adverse events case report form.

AEs will be assessed according to the CTCAE version 4.0 or the most current version. If CTCAE grading does not exist for an AE, the severity of the AE will be graded as mild (1), moderate (2), severe (3), life-threatening (4), or fatal (5).

Attribution of AEs will be indicated as follows:

- Definite: The AE is clearly related to the study drug
- Probably: The AE is likely related to the study drug
- Possible: The AE may be related to the study drug
- Unlikely: The AE is doubtfully related to the study drug
- Unrelated: The AE is clearly NOT related to the study drug

9.2 Serious Adverse Events

An AE is considered "serious" if, in the view of either the investigator or sponsor, it results in any of the following outcomes:

- Results in death,
- Is life threatening (an AE is considered "life-threatening" if, in the view of either the investigator or sponsor, its occurrence places the subject at immediate risk of death. It does not include an AE that, had it occurred in a more severe form, might have caused death.)
- Results in persistent or significant disability/incapacity or substantial disruption of the ability to conduct normal life functions,
- Results in congenital anomaly, or birth defect,
- Requires inpatient hospitalization or leads to prolongation of hospitalization (hospitalization for treatment/observation/examination caused by AE is to be considered as serious),
- Other medically important events.

9.3 Reporting of SAEs

Serious adverse events, whether or not considered drug related, should be reported to the lead site/sponsor (Duke) within 24 hours of becoming aware of the event, using the provided DCI SAE Report Form and the SAE Review Form (Site Assessment). These documents should be sent to:

The DCI Safety Desk – fax: (919)681-9357; phone: (919)681-9538; email: dcccsafe@dm.duke.edu

If the safety desk cannot be reached within 24 hours, the Principal Investigator should be contacted: Dr. Andrew Armstrong (phone: (919) 668-4615; pager: (919) 684-8111; email: andrew.armstrong@dm.duke.edu).

The initial report for each SAE or death should include at minimum the following information:

- Protocol # and title
- Patient initials, study identification number, sex, age
- Date the event occurred (onset)
- Description of the SAE
- Dose level and cycle number at the time the SAE occurred
- Description of the patient's condition
- Indication whether the patient remains on study
- Causality

Follow-up information including severity, action taken, concomitant medications, and outcome should be communicated to Duke as soon as possible.

Upon receipt of the Serious Adverse Event Reporting form by the DCI Safety Desk, the PI will be notified and be required to complete the PI assessment of the DCI Safety SAE Report Review Form. The DCI safety desk will, in turn, submit the SAE to the DUHS IRB if deemed reportable by the PI assessment. The DCI safety desk will also report the event to Pfizer as described below.

The following reportable events must be submitted to Pfizer within 24 hours (or immediately for death or life-threatening events) using the DCI SAE Report Form with *the Pfizer Reportable Events Fax Cover Sheet* with each SAE submission.

- **Serious Adverse Events**
- **Exposure during Pregnancy or Breastfeeding (even if not associated with an adverse event)**
- **Occupational exposure (even if not associated with an adverse event)**
- **Potential drug-induced liver injury (Hy's Law cases): These events are considered important medical events and should be reported as SAEs.**

The DCI SAE Report Form with the Pfizer Reportable Events Fax Cover Sheet should be emailed or faxed to:

Pfizer U.S. Clincal Trial Department
Email: USA.AEReporting@pfizer.com
Fax number: (866) 997-8322
The following minimum information is required:

- Protocol
- Site / PI
- Subject number, sex and age
- The date of report
- A description of the SAE (event, seriousness of the event)

Follow-up information for the event should be sent within promptly (within 7 days) as necessary.

In addition, if Principal Investigator becomes aware of an SAE occurring any time after the administration of the last dose of the Pfizer Product, Principal Investigator should report that SAE to Pfizer if the Principal Investigator suspects a causal relationship between the Pfizer Product and the SAE.

Reporting to the FDA
The Sponsor-Investigator (Duke) is responsible for reporting the serious adverse event to the FDA in accordance with 21CFR 312.32. Any SAE that is possibly related and unexpected must be submitted to the FDA attached to the IND.

9.4 Emergency Unblinding of Investigational Treatment

Not applicable

9.5 Procedure in case of pregnancy

Not applicable, only men will be enrolled in this study.

9.6 Safety Oversight Committee (SOC)

The Duke Cancer Institute SOC is responsible for annual data and safety monitoring of DUHS sponsor-investigator phase I and II, therapeutic interventional studies that do not have an independent Data Safety Monitoring Board (DSMB). The primary focus of the SOC is review of safety data, toxicities and new information that may affect subject safety or efficacy. Annual safety reviews includes but may not be limited to review of safety data, enrollment status, stopping rules if applicable, accrual, toxicities, reference literature, and interim analyses as provided by the sponsor-investigator. The SOC in concert with the DCI Monitoring Team oversees the conduct of DUHS cancer-related, sponsor-investigator therapeutic intervention and prevention intervention studies that do not have an external monitoring plan, ensuring subject safety and that the protocol is conducted, recorded and reported in accordance with the protocol, standing operating procedures (SOPs), Good Clinical Practice (GCP), and applicable regulatory requirements.

10 QUALITY CONTROL AND QUALITY ASSURANCE

10.1 Monitoring

This clinical research study will be monitored both internally by the PI and institutionally by the Duke Cancer Institute (DCI). In terms of internal review the PI will continuously monitor and tabulate adverse events. Appropriate reporting to the Duke University Medical Center IRB will be made. If an unexpected frequency of Grade III or IV events occur, depending on their nature, action appropriate to the nature and frequency of these adverse events will be taken. This may require a protocol amendment, dose de-escalation, or potentially closure of the study. The PI of this study will also continuously monitor the conduct, data, and safety of this study to ensure that:

- Interim analyses occur as scheduled;
- Stopping rules for toxicity and/or response are met;
- Risk/benefit ratio is not altered to the detriment of the subjects;
- Appropriate internal monitoring of AEs and outcomes is done;
- Over-accrual does not occur;
- Under-accrual is addressed with appropriate amendments or actions;
- Data are being appropriately collected in a reasonably timely manner.

DCI review and monitoring of this protocol occurs in accordance with the NCI-approved Data and Safety Monitoring Plan. Briefly, protocol review begins with an initial review by the Cancer Protocol Committee (CPC), which assesses the ethics and safety of the protocol. Documentation of these assessments will be maintained. Formal, independent monitoring will be conducted by the DCI Monitoring Team after the first 3 subjects are enrolled, followed by annual monitoring of 1-3 subjects until the study is closed to enrollment and subjects are no longer receiving study interventions that are more than minimal risk. DCI Monitoring Team reports and additional data/safety/toxicity reports submitted by the PI will be reviewed by the Safety Oversight Committee (SOC) on an annual basis. Additional monitoring may be prompted by findings from monitoring visits, unexpected frequency of serious and/or unexpected toxicities, or other concerns. Monitoring visits may also be initiated upon request by DUHS and DCI Leadership, CPC, SOC, the Duke Office of Audit, Risk and Compliance, a sponsor, an investigator, or the IRB. All study documents must be made available upon request to the DCI Monitoring Team and other authorized regulatory authorities, including but not limited to the National Institute of Health, National Cancer Institute, and the FDA. Every reasonable effort will be made to maintain confidentiality during study monitoring.

10.2 Data Management and Processing

10.2.1 Study Documentation

Study documentation includes but is not limited to source documents, case report forms, monitoring logs, appointment schedules, study team correspondence with sponsors or regulatory bodies/committees, and regulatory documents that can be found in the DCI-mandated "Regulatory Binder", which includes but is not limited to signed protocol and amendments, approved and signed informed consent forms, FDA Form 1572, CAP and CLIA laboratory certifications, and clinical supplies receipts and distribution records.

Source documents are original records that contain source data, which is all information in original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Source documents include but are not limited to hospital records, clinical and office charts, laboratory notes, memoranda, subjects' diaries or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate copies, microfiches, photographic negatives, microfilm or magnetic media, x-rays, subject files, and records kept at the pharmacy, at the laboratories and at medico-technical departments involved in the clinical trial. When possible, the original record should be retained as the source document. However, a photocopy is acceptable provided that it is a clear, legible, and an exact duplication of the original document.

10.2.2 Case Report Forms (CRFs)

The electronic CRF will be the primary data collection document for the study. The CRFs will be updated in a timely manner following acquisition of new source data. Only the key personnel delegated on the delegation of authority log are permitted to make entries, changes, or corrections in the CRF.

An audit trail will be maintained automatically by the electronic CRF management system. All users of this system will complete user training, as required or appropriate per regulations.

10.2.3 Data Management Procedures and Data Verification

Users of the electronic CRF will have access based on their specific roles in the protocol.

Completeness of entered data will be checked automatically by the eCRF system, and users will be alerted to the presence of data inconsistencies. Additionally, the data manager and project manager will cross-reference the data to verify accuracy. Missing or implausible data will be highlighted for the PI requiring appropriate responses (i.e. confirmation of data, correction of data, completion or confirmation that data is not available, etc.).

The database will be reviewed and discussed prior to database closure, and will be closed only after resolution of all remaining queries. An audit trail will be kept of all subsequent changes to the data.

10.2.4 Study Closure

Following completion of the studies, the PI will be responsible for ensuring the following activities:
- Data clarification and/or resolution
- Accounting, reconciliation, and destruction/return of used and unused study drugs
- Review of site study records for completeness
- Shipment of all remaining laboratory samples to the designated laboratories

11 STATISTICAL METHODS AND DATA ANALYSIS

All statistical analysis will be performed under the direction of the statistician designated in key personnel. Any data analysis carried out independently by the investigator must be approved by the statistician before publication or presentation.

11.1 Sample Size Estimation

This study will use the optimal two-stage design of Simon to test a hypothesis about response rate in subjects with NEPC treated with avelumab. Response will be defined as a complete (CR) or partial response (PR). Assuming that the response rate among subjects treated is 5%, the trial is designed to have 88% power with a one-sided type I error rate=5% to reject the null hypothesis of response rate of 5% when the true response rate was 20%. In the first stage, 18 subjects will be enrolled and if one or fewer responses are observed the trial will be terminated. However, if two or more responses are observed, an additional 26 subjects will be enrolled at the second stage for a total of 44 subjects. If five or more subjects respond, this new agent would be declared to have promising activity. This design has 88% power to conclude an agent is promising if its true objective response proportion is 20%; Type 1 error rate (one-sided) is 0.05 (this is the probability to conclude that a given agent is promising if its true objective response proportion is 5%).The probability of early termination under the null hypothesis is 0.77. These operating characteristics were selected to represent a reasonable compromise between high power, low false positive rates, and desire for small sample sizes, especially in the first stage. Allowing for 10% unevaluable rate, the target sample size is 49 subjects.

11.2 Analysis Sets

This is a non-blinded single arm-arm phase II study of approximately 49 subjects, to assess the safety and efficacy of avelumab in patients with mCRPC

11.3 Patient Demographics and Other Baseline Characteristics

Eligible men will have metastatic CRPC with NEPC phenotype with measureable disease at baseline.

11.4 Treatments

Avelumab with ADT (unless pure SCPC present) will start on cycle 1 day 1 and continue every 2 weeks until progression or unacceptable toxicity.

11.5 Primary Objective

To estimate the overall response rate of men with NEPC treated with avelumab as determined by modified PCWG3 using iRECIST radiographic response.

11.5.1 Variable

Overall response rate (ORR) which is defined as either complete response (CR) or partial response (PR).

11.5.2 Statistical Hypothesis, Model, Method of Analysis

The null hypothesis is that the ORR is less than 5%. The trial is designed to have 88% power with a one-sided type I error rate=5% to reject the null hypothesis when the true response rate was 20%. The objective response rate will be estimated with a standard error no greater than 10.7 percentage points.

11.5.3 Handling of Missing values, censoring, and discontinuations

Ineligible subjects and subjects who cancel registration before receiving any therapy will not be included in the analyses. We will follow each patient long enough to avoid censoring due to end of study. The binomial test assumes that other censoring than due to end of study is rare. The study results are just important reference and more studies are necessary for medical decision making.

11.6 Secondary Objectives

1. To describe the efficacy of PD-L1 inhibition with avelumab as measured by PCWG3 using RECIST1.1
2. To describe the radiographic progression free survival (rPFS) of PD-L1 inhibition with avelumab using immune modified and PCWG3-modified RECIST 1.1 criteria in this setting.
3. To describe the overall survival of PD-L1 inhibition in this setting.
4. To described the toxicities and safety of PD-L1 inhibition with avelumab in men with metastatic neuroendocrine-like prostate cancer.

11.6.1 Key Secondary Objectives – analysis plan

The Kaplan-Meier method will be used to estimate both forms of progression-free survival as well as the overall survival distributions. Summary statistic will be computed for the duration of time on treatment distribution. The correlative science analyses will be considered exploratory and interpreted as such and reported using descriptive statistics and associations with clinical outcomes including response (radiographic) and progression free and overall survival.

11.6.2 Other Secondary Objectives – Analysis Plan

In addition, descriptive statistics will be calculated for secondary endpoints of safety profile and quality-of-life (QOL) endpoints, the continuous safety and QOL endpoints will be summarized as the

patient counts, mean, standard deviation, median, 25thand 75th percentiles, minimum and maximum. The categorical safety and QOL endpoints will be categorized using frequencies and percentages.

11.7 Exploratory Objectives

1. To describe the impact of PD-L1 inhibition with avelumab on blood-based biomarker changes over time, including PSA, chromogranin-A, cell free DNA, LDH, and alkaline phosphatase.
2. To determine if levels of circulating biomarkers secreted by neuroendocrine-like prostate cancers correlate with clinical and radiographic treatment response
3. To determine if the presence of different immunohistochemical markers on the pre-biopsy specimens prognosticates clinical and radiographic treatment response
4. To determine if the level of different circulating immune cells correlate with both progressive addition of immunotherapy as well as clinical and radiographic treatment response or disease progression
5. To determine if levels of cell free DNA correlate with clinical and radiographic treatment response
6. To isolate prostate neuroendocrine-like CTCs for ex vivo growth and culture and characterization studies.

11.8 Interim Analysis

Not applicable

11.9 Accrual and Follow-Up

The target sample size is 18 subjects in stage 1, and 49 subjects overall if stage 1 is successful. Accrual is expected to be completed within 12-18 months after study activation for each stage. Stage 2 would require expansion to additional sites (2-3 additional sites) for accrual. All subjects will be followed for disease progression and mortality from the date that the subjects were enrolled to the protocol.

12 ADMINISTRATIVE AND ETHICAL CONSIDERATION

12.1 Regulatory and Ethical Compliance

This protocol was designed and will be conducted and reported in accordance with the International Conference on Harmonization (ICH) Harmonized Tripartite Guidelines for Good Clinical Practice, the Declaration of Helsinki, and applicable federal, state, and local regulations.

12.2 DUHS Institutional Review Board and DCI Cancer Protocol Committee

The protocol, informed consent form, advertising material, and additional protocol-related documents must be submitted to the DUHS Institutional Review Board (IRB) and DCI Cancer Protocol Committee (CPC) for review. The study may be initiated only after the Principal Investigator has received written and dated approval from the CPC and IRB.

The Principal Investigator must submit and obtain approval from the IRB for all subsequent protocol amendments and changes to the informed consent form. The CPC should be informed about any protocol amendments that potentially affect research design or data analysis (i.e. amendments affecting subject population, inclusion/exclusion criteria, agent administration, statistical analysis, etc.).

The Principal Investigator must obtain protocol re-approval from the IRB within 1 year of the most recent IRB approval. The Principal Investigator must also obtain protocol re-approval from the CPC within 1 year of the most recent IRB approval, for as long as the protocol remains open to subject enrollment.

12.3 Informed Consent

The informed consent form must be written in a manner that is understandable to the subject population. Prior to its use, the informed consent form must be approved by the IRB.

The Principal Investigator or authorized key personnel will discuss with the potential subject the purpose of the research, methods, potential risks and benefits, subject concerns, and other study-related matters. This discussion will occur in a location that ensures subject privacy and in a manner that minimizes the possibility of coercion. Appropriate accommodations will be made available for potential subjects who cannot read or understand English or are visually impaired. Potential subjects will have the opportunity to contact the Principal investigator or authorized key personnel with questions, and will be given as much time as needed to make an informed decision about participation in the study.

Before conducting any study-specific procedures, the Principal Investigator or designee must obtain written informed consent from the subject or a legally acceptable representative. The original informed consent form will be stored with the subject's study records, and a copy of the informed consent form will be provided to the subject.

12.4 Study Documentation

Study documentation includes but is not limited to source documents, case report forms (CRFs), monitoring logs, appointment schedules, study team correspondence with sponsors or regulatory bodies/committees, and regulatory documents that can be found in the DCI-mandated "Regulatory Binder", which includes but is not limited to signed protocol and amendments, approved and signed informed consent forms, FDA Form 1572, CAP and CLIA laboratory certifications, and clinical supplies receipts and distribution records.

Source documents are original records that contain source data, which is all information in original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Source documents include but are not limited to hospital records, clinical and office charts, laboratory notes, memoranda, subjects' diaries or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate copies, microfiches, photographic negatives, microfilm or magnetic media, x-rays, subject files, and records kept at the pharmacy, at

the laboratories and at medico-technical departments involved in the clinical trial. When possible, the original record should be retained as the source document. However, a photocopy is acceptable provided that it is a clear, legible, and an exact duplication of the original document.

A case report form (CRF) (please indicate whether a paper or electronic CRF will be used) will be the primary data collection document for the study. Only the key personnel delegated on the delegation of authority log are permitted to make entries, changes, or corrections in the CRF. For electronic CRFs, an audit trail will be maintained by the electronic CRF management system.

12.5 Privacy, Confidentiality, and Data Storage

The Principal Investigator will ensure that subject privacy and confidentiality of the subject's data will be maintained.

To protect privacy, every reasonable effort will be made to prevent undue access to subjects during the course of the study. All research related interactions with the participant will be conducted by qualified research staff who are directly involved in the conduct of the research study.

To protect confidentiality, subject files in paper format will be stored in secure cabinets under lock and key accessible only by the research staff. Electronic records of subject data will be maintained using a dedicated web-access secure database , which is housed in an encrypted and password-protected server behind the Duke firewall. Access to electronic databases will be limited to delegated personnel. The security and viability of the IT infrastructure will be managed by the DCI and/or Duke Medicine.

Upon completion of the study, research records will be archived and handled per institutional policy.

Subject names or identifiers will not be used in reports, presentations at scientific meetings, or publications in scientific journals

12.6 Data and Safety Monitoring

Data and Safety Monitoring will be performed in accordance with the external site Data and Safety Monitoring Plan, provided under separate cover.

12.7 Protocol Amendments

All protocol amendments must be initiated by the Principal Investigator and approved by the IRB prior to implementation. IRB approval is not required for protocol changes that occur to protect the safety of a subject from an immediate hazard. However, the Principal Investigator must inform the IRB and all other applicable regulatory agencies of such action immediately.

Though not yet required, the CPC should be informed about any protocol amendments that potentially affect research design or data analysis (i.e. amendments affecting subject population, inclusion/exclusion criteria, agent administration, etc.).

12.8 Records Retention

The Principal Investigator will maintain study-related records for a period of at least six years after study completion per Duke policy.

12.9 Conflict of Interest

The Principal Investigator and Sub-Investigators must comply with applicable federal, state, and local regulations regarding reporting and disclosure of conflict of interest. Conflicts of interest may arise from situations in which financial or other personal considerations have the potential to compromise or bias professional judgment and objectivity. Conflicts of interest include but are not limited to royalty or consulting fees, speaking honoraria, advisory board appointments, publicly-traded or privately-held equities, stock options, intellectual property, and gifts.

The Duke University School of Medicine's Research Integrity Office (RIO) reviews and manages research-related conflicts of interest. The Principal Investigator and Sub-Investigators must report conflicts of interest annually and within 10 days of a change in status, and when applicable, must have a documented management plan that is developed in conjunction with the Duke RIO and approved by the IRB/IEC.

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14 Appendix A: Performance Status Criteria

Karnofsky Performance Scale	
%	**Description**
100	Normal, no complaints, no evidence of disease
90	Able to carry on normal activity, minor signs or symptoms of disease
80	Normal activity with effort, some signs or symptoms of disease
70	Cares for self, unable to carry on normal activity or to do active work
60	Requires occasional assistance but is able to care for most needs
50	Requires considerable assistance and frequent medical care
40	Disabled, requires special care and assistance
30	Severely disabled, hospitalization indicated. Death not imminent.
20	Very sick, hospitalization indicated. Death not imminent.
10	Moribund, fatal processes progressing rapidly
0	Dead

15 Appendix B: FACT-P (version 4)

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

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

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

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

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

	FUNCTIONAL WELL-BEING	**Not at all**	**A little bit**	**Some-what**	**Quite a bit**	**Very much**
GF1	I am able to work (include work at home).....	0	1	2	3	4
GF2	My work (include work at home) is fulfilling	0	1	2	3	4
GF3	I am able to enjoy life	0	1	2	3	4
GF4	I have accepted my illness	0	1	2	3	4
GF5	I am sleeping well.....	0	1	2	3	4
GF6	I am enjoying the things I usually do for fun.....	0	1	2	3	4
GF7	I am content with the quality of my life right now	0	1	2	3	4

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

	ADDITIONAL CONCERNS	**Not at all**	**A little bit**	**Some-what**	**Quite a bit**	**Very much**
C2	I am losing weight	0	1	2	3	4
C6	I have a good appetite	0	1	2	3	4
P1	I have aches and pains that bother me	0	1	2	3	4
P2	I have certain parts of my body where I experience pain	0	1	2	3	4
P3	My pain keeps me from doing things I want to do	0	1	2	3	4
P4	I am satisfied with my present comfort level	0	1	2	3	4
P5	I am able to feel like a man	0	1	2	3	4
P6	I have trouble moving my bowels	0	1	2	3	4
P7	I have difficulty urinating	0	1	2	3	4
BL2	I urinate more frequently than usual	0	1	2	3	4
P8	My problems with urinating limit my activities	0	1	2	3	4
BL5	I am able to have and maintain an erection	0	1	2	3	4