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NCI Comprehensive Cancer Center
A Cancer Center Designated by the National Cancer Institute

STUDY NUMBER: CASE 6819

ClinicalTrials.gov NCT #: 04322643

Protocol Date: 7-17-2020

STUDY TITLE: A Phase II Study of Intermittent Checkpoint Inhibitor Therapy in Patients with Advanced Urothelial Carcinoma

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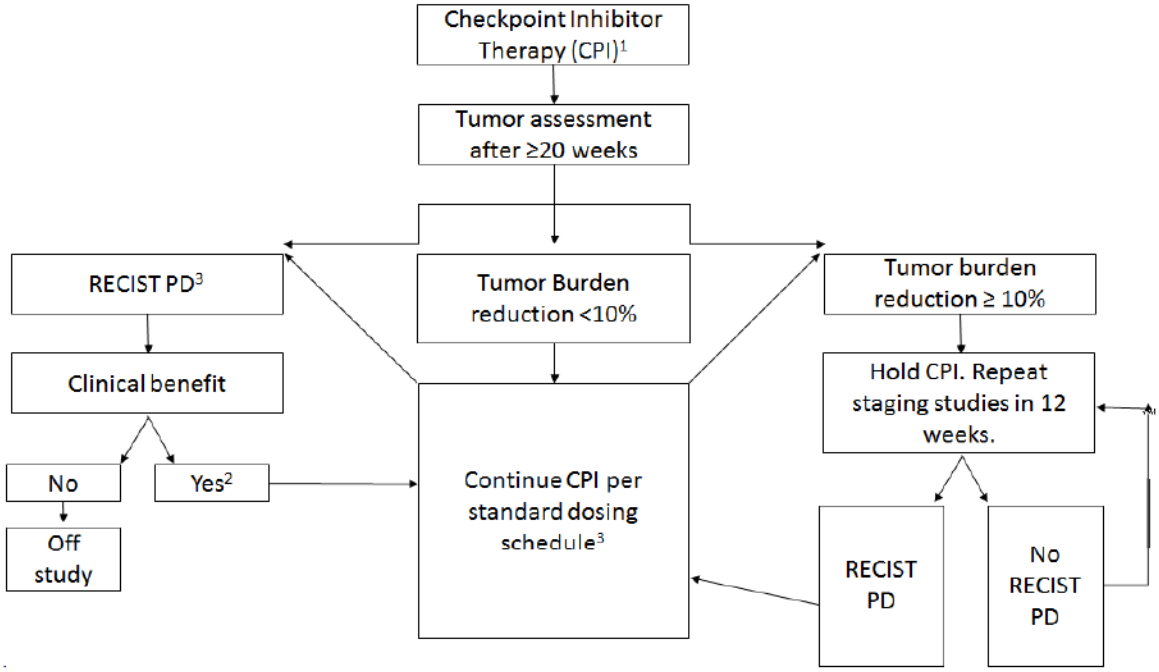
PRINCIPAL INVESTIGATOR SIGNATURE:

_____ Date: _____

SUMMARY OF CHANGES

Protocol Date	Section	Change
2/5/2020		Initial IRB approval
5/27/2020	Cover page	Added NCT number
		Protocol version date
	Footer throughout	Protocol version date
	Synopsis Section 3.0 Section 4.0	Changed eligibility to include all patients with advanced urothelial carcinoma who have received checkpoint inhibitors for a minimum of 20 weeks.
	Section 6 Section 9	Added option of new pembrolizumab dose (400mg every 6 weeks)
	Section 8.5	Added report on MedWatch FDA Form 3500A
	Section 11	Added a column in the calendar for schedule of visit/tests at the 6 week mark for patients who are OFF therapy
7/17/20	Section 4.1	Removed the following inclusion criteria: " Measurable disease as defined by RECIST 1.1 criteria." The rationale for this is that we are enrolling patients who have had good responses to therapy and as such some will – by definition, some will no longer have measurable disease.

STUDY SCHEMA



[1]Patients may be treated with any FDA-approved CPI for cisplatin-ineligible aUC or cisplatin resistant/refractory aUC.

[2]In cases where a patient is continued on therapy after PD and develops subsequent disease progression, CPI should be discontinued.

[3]Patients who do not have tumor burden reduction of >10% after 2 consecutive imaging will be removed from study.

* Of note all imaging is compared to scans done prior to intermittent therapy initiation.

PROTOCOL SUMMARY

Protocol Number/Title	CASE 6819 A Phase II Study of Intermittent Checkpoint Inhibitor Therapy In Patients With Advanced Urothelial Carcinoma
Study Phase	A Phase II study
Brief Background/Rationale	Immunotherapy has revolutionized the treatment of patients with aUC. Five checkpoint inhibitors (CPI) (atezolizumab, pembrolizumab, avelumab, durvalumab, and nivolumab) are approved for relapsed/refractory aUC following platinum-based chemotherapy and 2 CPI (atezolizumab and pembrolizumab) are approved for cisplatin-ineligible patients. Duration of therapy required to sustain clinical benefit is unclear; patients are treated indefinitely until intolerable toxicity or disease progression. Clinical trials investigating CPI in melanoma and kidney cancer have shown durable responses in patients who have discontinued therapy for reasons other than disease progression.[1,2] Similarly, in the CheckMate275 trial of nivolumab in patients with aUC who progressed following platinum-based chemotherapy, 6 patients had sustained responses off therapy (4–12+ weeks).[3] Likewise, in the phase 1/2 trial of durvalumab in aUC, a patient who discontinued treatment, unrelated to progression, maintained a response off therapy for >32 weeks.[4] Although generally well tolerated, the indefinite continuation of CPI presents multiple challenges including cumulative toxicities and financial burdens. Novel dosing schedules, early discontinuation considerations, and biomarkers of response are needed to identify patients who can sustain disease regression while off of therapy.
Primary Objective	To assess the efficacy of intermittent CPI therapy, defined as the proportion of patients who remain off therapy for at least 36 weeks
Secondary Objective(s)	• To determine the clinical outcome (TFI, ORR, PFS, OS) in advanced urothelial carcinoma with intermittent CPI therapy, at 12 week intervals from when therapy is first held. • To assess response to re-initiation of CPI therapy.
Exploratory Objective(s)	n/a
Correlative Objective(s)	Tissue: Investigate the genomic and immunologic markers of response and resistance to therapy. [See Section 10.2]

	Blood: Investigate the immunomodulatory cell makeup [specifically, lymphocyte PD-1 occupancy, myeloid-derived suppressor cells (MDSC), regulatory T cells (Treg), CD4 and CD8 T Cells, TCR repertoire] at the start of treatment, during the intermittent phase and off treatment. [See Section 10.1]
Sample Size	20 patients that have enrolled into the intermittent arm
Disease sites/Conditions	Advanced urothelial carcinoma
Interventions	A phase II study conducted investigating the use of intermittent CPI therapy in cisplatin ineligible or treatment refractory patients with aUC who respond to therapy. Patients will be treated with CPI therapy for at least 20 weeks as per standard of care (SOC), at which time those with a tumor burden reduction of 10% or greater will suspend CPI therapy. Patients with a documented increase in ≥ 20% tumor burden (RECIST 1.1 PD) will re-initiate CPI. For those patients who continue to have response, they will remain off therapy.

ABBREVIATIONS

CCCC	Case Comprehensive Cancer Center
CRF	Case Report Form
DSTC	Data Safety and Toxicity Committee
FDA	Food and Drug Administration
ICF	Informed Consent Form
IRB	Institutional Review Board
PRMC	Protocol Review and Monitoring Committee
SOC	Standard of Care
CCF	Cleveland Clinic Foundation
UH	University Hospitals
aUC	Advanced urothelial carcinoma
CPI	Checkpoint inhibitor
OS	Overall survival
PFS	Progression free survival
TFI	Treatment Free Interval
ORR	Overall response rate

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1.0 INTRODUCTION

1.1 Background of Advanced Urothelial Carcinoma and Standard Therapies

Bladder cancer is the sixth most common cancer in the US, with an estimated 81,190 new cases in 2018.[5] While the majority of cases are localized at initial diagnosis approximately 4% will present with *de novo* metastatic disease and another 40% of patients with localized disease will ultimately develop metastasis despite definitive therapy.[6–8] Advanced urothelial carcinoma (aUC) has a 5 year mortality rate exceeding 85%.[9,10]

The standard therapies for the front-line treatment of aUC are cisplatin based combinations, like methotrexate, vinblastine, doxorubicin, and cisplatin (MVAC) and gemcitabine with cisplatin, which demonstrate an overall response rate up to 50%, including approximately 10%–15% complete responses (CRs).[11,12] Almost half of urothelial cancer patients are unfit for cisplatin-containing chemotherapy due to impaired renal function, poor performance status or comorbidity. Prior to immunotherapy, the alternative option for cisplatin ineligible patients was gemcitabine with carboplatin or gemcitabine with paclitaxel. Outcomes are comparable to cisplatin based therapy with a median overall survival of 9-13 months.[1,5,613,14] Despite initial chemosensitivity, patients are not cured and the outcome of metastatic urothelial cancer after these regimens is poor: median time to progression is only 7 months and median overall survival (OS) is 15 months.[9,11] Second line chemotherapy has a limited role, but checkpoint inhibitors offer an additional option for patients who have progressed after initial systemic treatment.

1.2 Immunotherapy in Advanced Urothelial Carcinoma

Immunotherapy has revolutionized the treatment of patients with aUC. These therapies reverse innate immune inhibition by blocking programmed death 1 (PD-1), an inhibitory T-cell receptor, as well as targeting the co-inhibitory molecules programmed death ligands 1 and 2 (PD-L1 and PD-L2) expressed on tumor and other cells.[1,15] The expression of PD-1, PD-L1, and PD-L2 on their respective cells generates tumor resistance to the endogenous immune response resulting in tumor proliferation and growth. Blocking these resistance mechanisms with PD-1, PD-L1, and PD-L2 antibodies has the potential to enhance and unleash the host immune response against the tumor.[15,16]

Five CPI (atezolizumab, pembrolizumab, avelumab, durvalumab, and nivolumab) are approved for relapsed/refractory aUC following platinum-based chemotherapy and 2 CPI (atezolizumab and pembrolizumab) are approved for cisplatin-ineligible patients. Given its strong phase III data, pembrolizumab has become the default standard of care.

1.2.1 Pembrolizumab

In KEYNOTE-052, 370 patients with treatment naïve aUC were treated with pembrolizumab 200 mg every 3 weeks for up to two years. The average age was 74 years old, including 29% of patients older than 80 years. At a median follow up of 9.5 months, the ORR was 29%, including 7% of patients achieving CR.[17] Long term follow-up at 11.5 months, confirmed an ORR of 28.9% (95%CI 24.3-33.8) with 8.1% of patients achieving a CR. Median duration of response was still not reached and median OS was 11.5 mo

(95% CI 10.0-13.3). In PD-L1 positive tumors (combined positive score ≥ 10), ORR was 47.3% (95% CI 37.7-57.0) and median OS was 18.5 months (95%CI 12.2- NE). Other subgroups that had improved median OS was lymph node only disease (NR, 95%CI 24.0-57.0), ECOG PS 0/1 (13.1 mo; 95% CI 11.0-16.8), and ECOG 2 (9.7 mo; 95%CI 5.7-11.6). The most common any grade treatment related adverse events (TRAE) were fatigue (18.1%) and pruritis (17.8%). Immune related TRAE occurred in 24.6% of patients.[15] Based on these results, the FDA approved pembrolizumab in the front line setting for cisplatin ineligible, treatment naïve patients with aUC.

In KEYNOTE-045, patients with aUC refractory to cisplatin-based therapy were randomly assigned to either pembrolizumab (200 mg every 3 weeks for up to 2 years) versus investigator's choice of chemotherapy (including paclitaxel, docetaxel, or vinflunine). At a median follow up of 27.7 months, pembrolizumab showed improved OS (10.1 vs. 7.3 mo, HR 0.7; 95% CI 0.57-0.85, p< 0.0002), improved ORR (21% vs. 11%), improved duration of response (NR vs. 4.4 mo), less grade ≥3 toxicity (17% vs. 50%), and longer time to health-related quality of life deterioration (3.5 vs. 2.3 mo; HR 0.72).[18,19] There was no PFS benefit. Based on these results, pembrolizumab monotherapy is also approved in cisplatin refractory aUC.

1.2.2. Atezolizumab

IMvigor 210 was designed to investigate atezolizumab in both the front line and second line setting.

In cohort A, 119 cisplatin ineligible patients received atezolizumab 1200 mg every 3 weeks. At a median follow up of 17 months, ORR was 23%, including 9% CR and median OS was 15.9 months. At the time of analysis, median duration of response was not reached yet and 19 of 27 continued to have response.[20] 16% of patients experienced grade 3 or higher TRAE. Thus, atezolizumab is approved for front line therapy in platinum-intolerant patients.

In cohort B, 310 patients with metastatic urothelial carcinoma post-platinum treatment showed improved ORR 15% (compared to historical controls ORR 10%; p= 0.0058) regardless of PD-L1 status. Of the 45 responders, 84% had ongoing response at a median follow up of 11.7 months. Grade 3 or higher TRAE occurred in 16% of patients and immune mediated AE were 5% of patients; most notably pneumonitis, liver enzyme abnormalities, rash and dyspnea.[21] Patients who continued atezolizumab beyond progression had a longer post progression OS (8.6 months) compared to those transitioned immediately to different treatments (6.8 months) and those who did not have further treatment (1.2 months).[22] Based on these results, FDA granted accelerated approval for atezolizumab as a single agent as second-line treatment for subjects with locally advanced or metastatic urothelial carcinoma (mUC).

Of note, based on IMVigor 210, a phase III trial, IMvigor 211, randomized 931 patients, who had received platinum-based chemotherapy, to atezolizumab (1200 mg IV every 3 weeks) or to investigor's choice of second line chemotherapy (vinflunine, paclitaxel, or docetaxel). Atezolizumab had similar median OS (11.1 months vs. 10.6 months; p=0.41) and ORR (23% vs. 22%), but less grade 3 or higher TRAE (20% vs. 43%).[23] Atezolizumab remains approved as second line therapy despite these results.

1.2.3 Durvalumab

Durvalumab was explored in a phase I/II study, MEDI 4736, which looked at 191 patients with inoperable or metastatic urothelial cancer who had progressed during or after one standard platinum-based therapy. At a median follow up of 5.78 months, ORR was 17.8% (95% CI 12.7-24.0), including 7 patients who achieved CR. The median time of response was 1.41 months and median durable response had not yet been reached. Of note, patients with PD-L1 expression had better ORR (27.6% vs. 5.1%), median PFS (1.5 mo, 95%CI 1.4-1.9 mo) and median OS (18.2 mo, 95%CI 8.1-NE). Additionally, durvalumab was found to be well tolerated with only 6.8% of patients experiencing a grade 3 or more TRAE and 2.1% of patients having grade 3 or more immune TRAE, most notably hepatitis and pneumonitis.[4]

1.2.4. Nivolumab

In Checkmate 032, an open label, multicenter phase 1/2 expansion cohort study in patients with aUC, who had progressed after previous platinum based therapy, showed nivolumab was associated with a substantial and durable clinical response. At a minimum follow up of 9 months, 19 of 78 (24.4%) of patients had an objective response, with 17.9% achieving CR. The median duration of response was 9.4 months (IQR 5.7-12.5) and the median time to response was 1.5 months (IQR 1.2-4.1). Interestingly, four patients were able to sustain response after nivolumab monotherapy discontinuation (7-22+ weeks).[24]

In the phase II CheckMate 275 trial, 265 previously treated aUC patients were treated with nivolumab 3 mg/kg IV every 2 weeks until progression or unacceptable toxicity. The ORR was 19.6%. (95% CI 0-24.9) with 2% of patients achieving a CR. The median duration of response was NR, with 77% of patients having an ongoing response and the median OS was 8.74 mo (95% CI 6.05 to NR).[3]

1.2.5 Avelumab

Avelumab is another PD-L1 inhibitor that has shown benefit in the platinum-refractory space. In a phase 1b trial, avelumab 10mg/kg IV every 2 weeks. At a median follow up of 16.5 months, ORR was 18.2% (95%CI 8.2%-32.7%) with 5 CR. The median duration of response was NR (95%CI 12.1 weeks to NE) and responses were ongoing in 6 patients (75.0%). Of note, 7 of 8 of the responders were PD-L1 positive (IHC ≥ 5% of tumor cells). There was also an improvement in median PFS (11.6 weeks, 95% CI, 6.1 to 17.4 weeks), median OS (13.7 months, 95% CI, 8.5 months to NR), and 12-month OS rate (54.3%, 95% CI, 37.9% to 68.1%).[25] Based on a pooled analysis of the two expansion cohorts in the above JAVELIN solid tumor trial, avelumab was approved for the treatment of platinum refractory aUC based on a pooled analysis of two expansion cohorts in the above JAVELIN solid tumor trial.[26]

1.3 Rationale

An unanswered question with the use of CPI is the duration of therapy required for optimal clinical benefit. In the absence of progressive disease or unacceptable toxicities, there are currently no specified criteria for treatment discontinuation. Strategies to reduce toxicity and maximize benefit require investigation. Clinical trials investigating CPI in melanoma and kidney cancer have shown durable responses in patients who have

discontinued therapy for reasons other than disease progression.[16,27,28] In fact, our group conducted a phase II trial of intermittent nivolumab in aRCC and showed not only was it feasible but that at 48 weeks, 4 out of 5 patients were able to sustain response off therapy.[28]

Similarly, in bladder cancer, in Checkmate 032, four patients were able to sustain response after nivolumab monotherapy discontinuation (7-22+ weeks).[24] Additionally, in the CheckMate275 trial of nivolumab in patients with aUC who progressed following platinum-based chemotherapy, 9 patients had sustained responses off therapy 2–17+ weeks.[3] Likewise, in MEDI 4736, there was a patient who discontinued treatment, unrelated to progression, and maintained a response for >32 weeks.[4]

In general, most patients can achieve a response to any of the 5 approved CPI therapies within 2 months of treatment initiation (range 1.4-2.85 months).[3,4,17,19,21,23–26] Specifically with pembrolizumab, in both cisplatin refractory and cisplatin ineligible patients, the median response time to response was 2-2.1 months and the percentage of patients who responded to pembrolizumab and did not have PD at 1 year was 68% (median duration of response was 1.6+- 30.3+ months.).[17,19,29] Phase I data in refractory solid tumors showed that regardless of dose, a single IV infusion of nivolumab (0.3-10mg/kg IV) lead to a serum half-life of 12-20 days with a mean plateau PD-1 receptor occupancy on peripheral blood circulating T cells of 72% (range 59-81%) for greater than 57 days.[16] Similar findings were seen in cohort A of a study of melanoma, RCC, and UC, where responders (RECIST CR, PR or SD) had sustained PD-1 receptor occupancy (>80% for up to 300 day) despite non-detectable serum nivolumab levels.[30] A review of the pharmacodynamics of all 5 CPI show a flat exposure to response relationship with >70% target receptor saturation (range 70%-99%).[31] This data suggests that nivolumab has a high affinity for PD-1 and that sufficient concentrations persist to maintain plateau occupancy even when serum levels are not detectable. These studies suggest that those who respond to checkpoint inhibitor therapy do so quickly and potentially could have durable responses.

Along with physical toxicity, financial toxicity is a real concern for treatments with an indefinite time course. The average cost of one dose of any CPI therapy is $8,791.60, with a yearly cost ranging from $169,911 to $200,865.[32] These values do not account for the cost of toxicity management that may incur. In an era of health-care cost containment and documented financial burden of cancer therapy to patients and the health-care system, it is particularly important to develop treatment regimens and schedules that reduce cost.

Thus, novel dosing schedules, early discontinuation considerations, and biomarkers of response are needed to identify patients who can sustain disease regression while off of therapy. Similar to the RCC study we previously conducted, we hypothesize that there is a subgroup of patients with advanced urothelial carcinoma who are able to sustain response off of CPI therapy.

1.4 Background and rationale of correlative studies

Immunotherapy functions to modulate the immune microenvironment. Myeloid derived suppressor cells (MDSC), $CD8^+$ and $CD4^+$ T cells, regulatory T cells (Tregs), T cell receptor (TCR) repertoire, among others are important contributors both to the

function of and resistance to targeted therapy and immunotherapy.[33-36] For example, in melanoma, patients with higher numbers of circulating T_{reg} cells and T_{eff} cells after CPI therapy were predictive of treatment responses.[37,38] CPI therapy was also associated with changes to the TCR repertoire, which is crucial to T cell functioning.[39] Additionally, in breast and colon cancer, MDSC levels have correlated with treatment response, disease progression, and clinical outcomes.[34] Specifically in urothelial carcinoma, MDSCs in peripheral blood have been correlated with pathology and response to CPI therapies.[40,41]

The tumor microenvironment as well as the peripheral blood are dynamic and subject to change based on changes in tumor burden and therapy. There is a lack of prospective data demonstrating correlations between changes in peripheral blood and changes in the tumor microenvironment. The goal of this study is to generate a hypothesis that changes in the type and behavior of immunomodulatory cells in the peripheral blood will reflect tumor burden and that such changes will impact tumor burden while on CPI therapy. The presence of a biomarker (or composite biomarker score) to identify patients likely to benefit from CPI will help prospectively select patients for therapy. Likewise, the development of biomarkers to determine which patients are likely to tolerate extended breaks from therapy without compromising efficacy, will minimize toxicity for select patients.

Another point of interest would be to evaluate the rate at which the PD-1 receptor occupancy on peripheral blood circulating T cells changes over time with CPI suspension. Previous studies have shown PD-1 receptors can remain occupied for >10 months despite non-detectable levels in the blood.[31] This is potentially a reason why patients have "durable" responses and slow resolving toxicities to immunotherapy even after discontinuation. Understanding the pharmacodynamics of anti-PD-1/anti-PD-L1 therapy on PD-1 receptor occupancy is crucial in developing a dose suspension schedule.

Based on our current knowledge these are the correlatives we are interested in and will pursue as long as it is still clinically relevant.

2.0 OBJECTIVES

2.1 Primary Objective

To assess the efficacy of intermittent CPI therapy, defined as the proportion of patients who remain off therapy for at least 36 weeks

2.2 Secondary Objective(s)

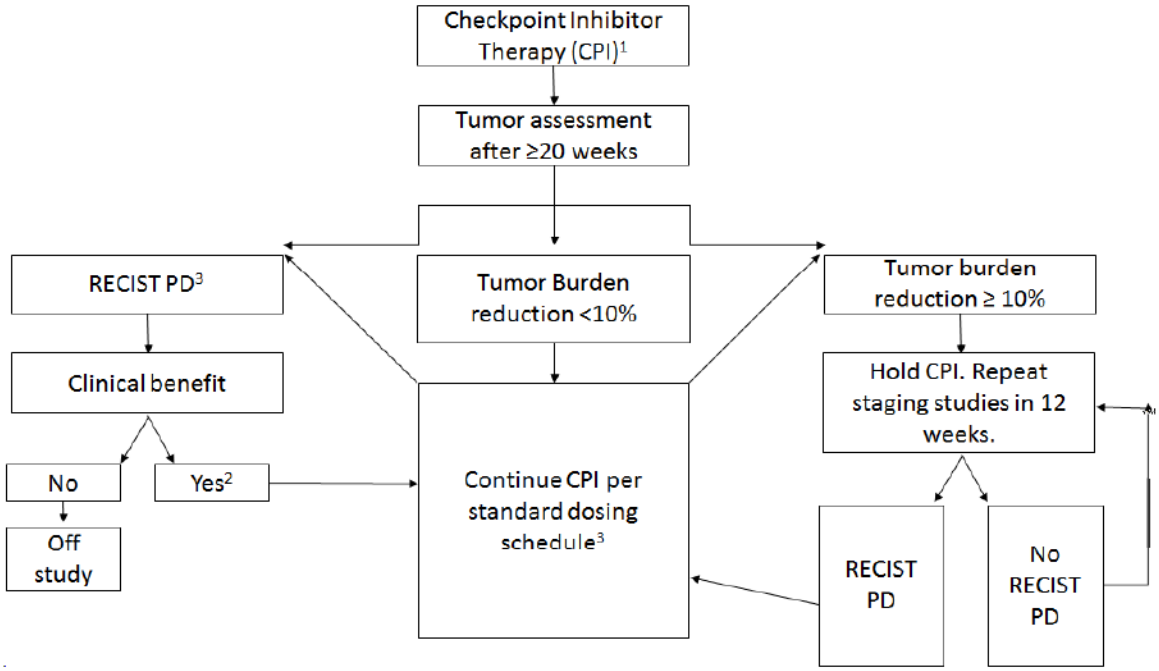
- To determine the clinical outcome (TFI, ORR, PFS, OS) in advanced urothelial carcinoma with intermittent CPI therapy.
- To assess response to re-initiation of CPI therapy

2.3 Correlative Objective(s)

- Tissue: Investigate the genomic and immunologic markers of response and resistance to therapy.
- Blood: Investigate the immunomodulatory cell makeup [specifically, lymphocyte PD-1 occupancy, myeloid-derived suppressor cells (MDSC), regulatory T cells (Treg), CD4 and CD8 T Cells, TCR repertoire] at the start of treatment, during the intermittent phase and off treatment

3.0 STUDY DESIGN

3.1 Study design including dose escalation / cohorts



[1]Patients may be treated with any FDA-approved CPI for cisplatin-ineligible aUC or cisplatin resistant/refractory aUC.

[2]In cases where a patient is continued on therapy after PD and develops subsequent disease progression, CPI should be discontinued.

[3]Patients who do not have tumor burden reduction of >10% after 2 consecutive imaging will be removed from study.

* Of note all imaging is compared to scans done prior to intermittent therapy initiation.

A phase II study design to investigate the use of any CPI on an intermittent dosing schedule. Patients with aUC who treatment refractory or cisplatin ineligible will receive CPI of choice as per standard dosing. Patients who have initial ≥ 10% tumor burden

reduction will discontinue the CPI until they experience a ≥20% disease progression, at which time CPI therapy will be restarted.

The 10% cut off was chosen on the basis of a metanalysis in CPI-treated metastatic melanoma that this cut point may optimally separate overall survival in patients (better than the traditional RECIST PR 30% cut off) and also from prior experience using this cut off in an intermittent nivolumab trial in kidney cancer.[28,42] Please refer to section 14.0 for statistical consideration, including early stopping rules.

3.2 Number of Subjects

Our goal is to enroll 20 CPI-eligible patients onto the intermittent arm. We will first screen up to 50 patients for this study in order to get our target sample size. If, there are not at least 20 patients with a tumor burden reduction of 10% or greater, we will continue to screen up to 25 more patients (total of 75 patients). If we screen 75 patients without enrolling 20 patients into the intermittent arm, we will stop the trial and deem it not feasible (refer to section 14.1 for sample size justification)

3.3 Expected Duration of Treatment and Subject Participation

Each study cycle consists of 14-28 days, depending on which CPI is chosen. CPI of choice will be administered on day 1.

All patients who do not meet criteria for the CPI intermittent phase of the study will be treated until unacceptable toxicity or RECIST-defined PD. Patients with RECIST-defined PD may continue CPI therapy at the discretion of the treating MD. These patients will continue with normal imaging every 12 weeks. In cases where a patient is continued on therapy after PD and develops subsequent PD (≥ 20% increase in sum of target lesions compared to the initial PD tumor measurements, the patient will come off study).

Patients who meet criteria for the intermittent phase (i.e., have ≥10% tumor burden reduction) will not receive CPI therapy. Imaging will continue per protocol (every 12 weeks from the initial date they stopped CPI therapy). Patients who have RECIST defined PD on the intermittent phase should reinitiate CPI therapy. Patients who have a subsequent decrease in tumor burden ≥ 10% can then restart CPI therapy as per protocol. (refer to schema in Section 3.1).

4.0 SUBJECT SELECTION

Each of the criteria in the sections that follow must be met in order for a subject to be considered eligible for this study. Use the eligibility criteria to confirm a subject's eligibility.

4.1 Inclusion Criteria

Patients must meet all the following criteria to be eligible for study enrollment.

- Men and women ≥ 18 years of age.

- Histological confirmation of urothelial carcinoma (any histology)
- Advanced or metastatic urothelial carcinoma.
- Has received at least 20 weeks on CPI therapy per standard of care (SOC) for advanced urothelial carcinoma
- Karnofsky Performance Score (KPS) ≥70% (for more information on KPS, please see: http://www.npcrc.org/files/news/karnofsky_performance_scale.pdf)
- Willing and able to provide informed consent.
- Laboratory criteria for study entry must meet the following criteria:
    - Serum creatinine ≤ 2 x ULN OR CrCl ≥ 30 mL/min (measured or calculated using the Cockcroft-Gault formula).
    - Hb ≥ 8.0g/dL
    - AST and ALT ≤ 3.0 x ULN
    - Bilirubin ≤ 1.5 x ULN (except subjects with Gilbert Syndrome, who can have total bilirubin < 3.0 mg/dL)

4.2 Exclusion Criteria

The presence of any of the following will exclude a patient from study enrollment:

- History of severe hypersensitivity reaction to any monoclonal antibody.
- Patients are excluded if they have known HIV/AIDS.
- Major surgery (eg, cystectomy) less than 28 days prior to the first dose of study drug.
- Any condition requiring systemic treatment with either corticosteroids (> 10 mg daily prednisone equivalent) or other immunosuppressive medications within 7 days prior to the first dose of study drug. Inhaled steroids and adrenal replacement steroid doses > 10 mg daily prednisone equivalent are permitted in the absence of active autoimmune disease.
- Known medical condition (eg, a condition associated with diarrhea or acute diverticulitis) that, in the investigator's opinion, would increase the risk associated with study participation or study drug administration or interfere with the interpretation of safety results.
- Pregnant women are excluded from this study because animal studies have demonstrated that PD-1/PD-L1 inhibitors can cause fetal harm when administered to pregnant women. Breastfeeding women are excluded from this study because PD-1/PD-L1 inhibitors may be excreted in human milk and the potential for serious adverse reactions in nursing infants.[43]

4.3 Inclusion of Women and Minorities

Men, women and members of all races and ethnic groups are eligible for this trial.

5.0 REGISTRATION

All subjects who have been consented are to be registered in the OnCore® Database. For those subjects who are consented, but not enrolled, the reason for exclusion must be recorded.

All subjects will be registered though Cleveland Clinic Lead Study Coordinator and will be provided a study number by contacting the study coordinator. In the event that the Lead Study Coordinator cannot be reached, the Database Manager may be contacted to register a patient. Contact information for these individuals is listed below.

Title	Name	Phone	Email
Lead Study Coordinator	[redacted]	[redacted]	[redacted]
Database Manager	[redacted]	[redacted]	[redacted]

6.0 TREATMENT PLAN

6.1 Checkpoint Inhibitor Treatment Regimen Overview

Treatment will be administered on an outpatient basis and administered as the following:

- Pembrolizumab 200 mg IV over 30 minutes every 3 weeks
- Pembrolizumab 400 mg IV over 30 minutes every 6 weeks (Decision on pembrolizumab dose will be based on provider discretion).
- Atezolizumab 1200 mg IV over 60 minutes every 3 weeks. (if first dose is tolerated, all subsequent infusions may be delivered over 30 minutes)
- Durvalumab 10 mg/kg IV over 60 minutes every 2 weeks.
- Nivolumab 480mg IV over 30 minutes every 4 weeks
- Avelumab 800 mg IV over 60 minutes every 2 weeks

*Please refer to Section 9.0 for further pharmaceutical details.

6.2 Checkpoint Inhibitor Reactions: follow Institutional guidelines. In the absence of any such guidelines, or per provider discretion, apply the following:

For Grade 1 symptoms: Mild reaction; itching, rash, hives, fever, rigors): Stop the infusion, notify provider and study nurse. Initiate normal saline infusion at 500ml/hr, titrate up to maintain systolic BP >100. Administer diphenhydramine 50mg IV. Remain at bedside and monitor subject until recovery from symptoms.

The following prophylactic pre-medications are recommended for future infusions: diphenhydramine 50 mg (or equivalent) and/or paracetamol 325 to 1000 mg (acetaminophen) at least 30 minutes before additional CPI administrations.

For Grade 2 symptoms: Moderate reaction such as SOB, chest tightness, back pain, which requires therapy or infusion interruption but responds promptly to symptomatic treatment Follow above for Grade 1 and add oxygen at 2L via nasal cannula and titrate to

keep O2 saturation > 92% and give hydrocortisone 100mg IVP once; remain at bedside and monitor subject until resolution of symptoms. If symptoms progress, do not re-dose medications already given, move on to treatment for severe / Grade 3 reactions. If the infusion is interrupted, then restart the infusion at 50% of the original infusion rate when symptoms resolve; if no further complications ensue after 30 minutes, the rate may be increased to 100% of the original infusion rate.

Monitor subject closely. If symptoms recur, then no further CPI will be given. Diphenhydramine 50 mg IV and remain at bedside and monitor the subject until resolution of symptoms. The amount of study drug infused must be recorded on the electronic case report form (eCRF). The following prophylactic pre-medications are recommended for future infusions: diphenhydramine 50 mg (or equivalent) and/or paracetamol 325 to 1000 mg (acetaminophen) should be administered at least 30 minutes before additional CPI administrations. If necessary, corticosteroids (recommended dose: up to 25 mg of IV hydrocortisone or equivalent) may be used.

For Grade 3 or Grade 4 symptoms: (Severe reaction, anaphylaxis, bronchospasm, stridor, wheezing, respiratory distress, angioedema, systolic BP < 80mm Hg, or LOC. Grade 3: prolonged [ie, not rapidly responsive to symptomatic medication and/or brief interruption of infusion] recurrence of symptoms following initial improvement; hospitalization indicated for other clinical sequelae [eg, renal impairment, pulmonary infiltrates]). Grade 4: (life threatening; pressor or ventilatory support indicated): Immediately discontinue infusion of nivolumab. Follow guidelines for Grades 1 and 2 and add the following: Activate emergency response team as appropriate. Administer medications from Grade 1 and 2 reaction guidelines if not yet given and add Epinephrine 0.2 to 1 mg of a 1:1,000 solution for subcutaneous administration or 0.1 to 0.25 mg of a 1:10,000 solution. Subject should be monitored until the investigator is comfortable that the symptoms will not recur. CPI will be permanently discontinued.

In the case of late-occurring hypersensitivity symptoms (eg, appearance of a localized or generalized pruritis within 1 week after treatment), symptomatic treatment may be given (eg, oral antihistamine, or corticosteroids).

6.3 General Concomitant Medications and Supportive Care Guidelines

The following medications are prohibited during the study:

- Any concurrent antineoplastic therapy (ie, chemotherapy, hormonal therapy, immunotherapy, extensive radiation therapy, or standard or investigational agents for treatment of cancer).

Palliative (limited-field) radiation therapy is permitted, if all of the following criteria are met:

- The lesion being considered for palliative radiation is not a target lesion.

6.4 Criteria for Removal from Study

Patients will be treated per protocol until:

1. RECIST-PD (treating MD may continue CPI). Study PI must be informed via email (or Site Communication Form") that subject is continuing based on clinical benefit. These patients will continue per normal imaging schedule (every 12 weeks).
2. Patients on CPI treatment who develop a RECIST-PD (PD1) can continue CPI treatment if there is clinical benefit. If on subsequent imaging they continue to have RECIST-PD (PD2), they will be removed from trial.
3. Unacceptable toxicity (see Section 7.3)
4. Withdrawal of consent
5. General or specific changes in the patients' condition that render the patient unacceptable for further treatment in the judgment of the investigator.
6. Any patient who on consecutive imaging (i.e., for 24 weeks) has SD while on therapy and does not achieve > 10% tumor burden reduction will be removed from the trial.

6.5 Duration of Follow Up

Patients will continue to be followed for at least 30 days after the last dose of trial drug or until new anti-cancer treatment is initiated, whichever is earlier.

7.0 DOSE DELAYS / DOSE MODIFICATIONS

Patients will be monitored closely for toxicity and dose delays will be implemented where clinically necessary as per the ASCO guideline: Management of Immune-Related Adverse Events in Patients Treated with Immune Checkpoint Inhibitors. (For more information, please see: https://ascopubs.org/doi/full/10.1200/JCO.2017.77.6385) No dose modifications are permitted.)

7.1 Dose Delay Criteria

CPI administration should be withheld for the following:

1. Any grade 3 drug-related AE
2. Any drug-related AE requiring the initiation of prednisone >10 mg per day (or equivalent steroid dose).
3. Any AE, laboratory abnormality, or intercurrent illness which, in the judgment of the investigator, warrants delaying the dose of study medication.

7.2 Criteria to Resume Treatment

Subjects may resume treatment when the following criteria are met

1. Subjects may resume treatment when any drug-related laboratory or clinically AE revert to grade 1 or less.
2. Any AE that in the judgment of the investigator has sufficiently resolved.
3. Prednisone < 10mg per day (or equivalent steroid dose).

7.3 Discontinuation Criteria

Treatment should be permanently discontinued for the following:

1. Any grade 4 drug-related AE warrants permanent discontinuation, unless it is a reversible endocrinopathy.
2. Any adverse event, laboratory abnormality, or intercurrent illness which, in the judgment of the Investigator, presents a substantial clinical risk to the subject with continued CPI dosing

8.0 ADVERSE EVENTS AND POTENTIAL RISKS

8.1 Adverse Event Definition

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

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

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

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

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

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

8.2 Serious Adverse Events Definition

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

- results in death
- is life-threatening (defined as an event in which the subject was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe)
- requires inpatient hospitalization or causes prolongation of existing hospitalization (see NOTE below)
- results in persistent or significant disability/incapacity
- is a congenital anomaly/birth defect
- is an important medical event (defined as a medical event(s) that may not be immediately life-threatening or result in death or hospitalization but, based upon appropriate medical and scientific judgment, may jeopardize the subject or may require intervention [eg, medical, surgical] to prevent one of the other serious outcomes listed in the definition above.) Examples of such events include, but are not limited to, intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization.)
- Potential drug induced liver injury (DILI) is also considered an important medical event.
- Suspected transmission of an infectious agent (eg, pathogenic or nonpathogenic) via the study drug is an SAE.
- Although pregnancy, overdose, and cancer are not always serious by regulatory definition, these events must be handled as SAEs.

8.3 Non-Serious Adverse Events Definition

- A non-serious adverse event is an AE not classified as serious.

8.4 Adverse Event Evaluation

The collection of Grade ≥2 AE and SAE information should begin at initiation of study drug. All non-serious adverse events (not only those deemed to be treatment-related) should be collected continuously during the treatment period and for a minimum of 30 days following the last dose of study treatment or until next treatment is initiated, whichever comes first.

Baseline physical and laboratory Grade ≥2 AEs should be followed to resolution or stabilization or reported as SAEs if they become serious. Follow-up is also required for non-serious AEs that cause interruption or discontinuation of study drug and for those present at the end of study treatment as appropriate.

A laboratory test abnormality considered clinically relevant (e.g., causing the subject to withdraw from the study, requiring treatment or causing apparent clinical manifestations, result in a delay or dose modification of study treatment, or judged relevant by the investigator), should be reported as an adverse event.

The investigator or sub-investigator (treating physician if applicable) will provide the following for all adverse events (both serious and non-serious):

- Event term (as per CTCAE)
- Description of the event
- Date of onset and resolution
- Expectedness of the toxicity
- Grade of toxicity
- Attribution of relatedness to the investigational agent- (this must be assigned by an investigator, sub-investigator, or treating physician)
- Action taken as a result of the event, including but not limited to; no changes, dose interrupted, reduced, discontinued, etc. or action taken with regard to the event, i.e. no action, received conmed or other intervention, etc.
- Outcome of event

Descriptions and **grading scales** found in the NCI Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 will be utilized for AE reporting. (for more information, please see https://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm#ctc_50)

An **expected adverse event** is an event previously known or anticipated to result from participation in the research study or any underlying disease, disorder, or condition of the subject. The event is usually listed in the Investigator Brochure, consent form or research protocol.

An **unexpected adverse event** is an adverse event not previously known or anticipated to result from the research study or any underlying disease, disorder, or condition of the subject.

Attribution is the relationship between an adverse event or serious adverse event and the study drug. Attribution will be assigned as follows:

- Definite – The AE is clearly related to the study drug.
- Probable – 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.

Protocol must specify if attribution is required for individual components of the treatment regimen or the treatment regimen as a whole.

8.5 Reporting Procedures for Serious Adverse Events and OnCore®

Following the subject's written consent to participate in the study, all SAEs, whether related or not related to study drug, must be collected, including those thought to be

associated with protocol-specified procedures. All SAEs must be collected that occur within 30 days of discontinuation of dosing or until next treatment is initiated

All SAEs must be collected that occur during the screening period. If applicable, SAEs must be collected that relate to any protocol-specified procedure (eg, a follow-up skin biopsy). All SAEs should be monitored until they are resolved or are clearly determined to be due to a subject's stable or chronic condition or intercurrent illness(es). The investigator should report any SAE that occurs after these time periods that is believed to be related to study drug or protocol-specified procedure.

SAEs will be recorded on the FDA Form 3500A (MedWatch) according to the reporting guidelines in section 8.5.

8.6 Serious Adverse Events and OnCore®
All SAEs will be entered into OnCore.

8.7 Reporting Procedures for Serious Adverse Events and OnCore®
It is the responsibility of each site PI to ensure that ALL SAEs occurring on this trial (internal or external) are reported to the Case Comprehensive Cancer Center's Data and Safety Toxicity Committee. This submission is simultaneous with their submission to the sponsor and/or other regulatory bodies.

The sponsor-investigator is responsible for submitting an annual report to the DSTC as per CCCC Data and Safety Monitoring Plan.

8.8 Data and Safety Monitoring Plan
This protocol will adhere to the policies of the Case Comprehensive Cancer Center Data and Safety Monitoring Plan in accordance with NCI guidelines.

9.0 PHARMACEUTICAL INFORMATION

9.1 Pembrolizumab Product Information

Product description and dosage form	Potency	Primary Packaging (volume)/Label type	Appearance	Storage condition (per label)
Pembrolizumab Solution for Injection	100 mg/Vial (25 mg/mL)	4 mL type 1 flint glass vials	Clear to opalescent, colorless to pale yellow liquid. May contain particles	Stores at 2 to 8 degrees Celsius (36 to 46 degrees Fahrenheit) and protected from light and freezing.

Please refer to FDA package insert for further details.
(https://www.accessdata.fda.gov/drugsatfda_docs/label/2016/125514s012lbl.pdf)

Pembrolizumab will be given every three weeks at a dose of 200 mg to be administered as a 30 minute IV infusion. Pembrolizumab can also be given every six weeks at a dose of 400 mg to be administered as a 30 minute IV infusion. Decision on pembrolizumab dose will be based on provider discretion.

Subjects may be dosed every 21 days (or 42 days for 400mg dose) +/- 3 days from the previous dose of drug. There are no premedications recommended for pembrolizumab on the first cycle. Subjects should be carefully monitored for infusion reactions during pembrolizumab administration. If an acute infusion reaction is noted, subjects should be managed according to Section 6.1.

9.2 Atezolizumab Product information

Product description and dosage form	Potency	Primary Packaging (volume)/Label type	Appearance	Storage condition (per label)
Atezolizumab Solution for injection	1200 mg/Vial (60 mg/mL)	20 mL type 1 flint glass vials	Clear to opalescent, colorless to pale yellow liquid. May contain particles	Stores at 2 to 8 degrees Celsius (36 to 46 degrees Fahrenheit) and protected from light and freezing.

Please refer to FDA package insert for further details.
(https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/761034s010lbl.pdf)

Atezolizumab will be given every three weeks at a dose of 1200 mg to be administered as a 60 minute IV infusion. If the first infusion is tolerated, all subsequent infusions may be delivered over 30 minutes.

Subjects may be dosed every 21 days +/- 3 days from the previous dose of drug. There are no premedications recommended for atezolizumab on the first cycle. Subjects should be carefully monitored for infusion reactions during atezolizumab administration. If an acute infusion reaction is noted, subjects should be managed according to Protocol Section 6.1.

9.3 Durvalumab Product Information

Product description and dosage form	Potency	Primary Packaging (volume)/Label type	Appearance	Storage condition (per label)
Durvalumab Solution for Injection	500 mg/vial (50 mg/mL) 120 mg/vial (50 mg/mL)	10 mL type 1 flint glass vials 2.4 mL type 1 flint glass vials	Clear to opalescent, colorless to pale yellow liquid. May contain particles	Stores at 2 to 8 degrees Celsius (36 to 46 degrees Fahrenheit) and protected

				from light and freezing. 4 hours at room temperature up to 25 degree Celsius (77 degree Fahrenheit)

Please refer to FDA package insert for further details.
(https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/761069s000lbl.pdf)

Durvalumab will be given every 2 weeks at a dose of 10 mg/kg to be administered as a 60 minute IV infusion.

Subjects may be dosed every 14 days +/- 2 days from the previous dose of drug. There are no premedications recommended for durvalumab on the first cycle. Subjects should be carefully monitored for infusion reactions during durvalumab administration. If an acute infusion reaction is noted, subjects should be managed according to Protocol Section 6.1.

9.4 Nivolumab Product Information

Product description and dosage form	Potency	Primary Packaging (volume)/Label type	Appearance	Storage condition (per label)
Nivolumab Solution for Injection	100 mg/Vial (10 mg/mL) 40 mg/vial (10 mg/mL) 240 mg/vial (10 mg/mL)	10 mL type 1 flint glass vials 4 mL type 1 flint glass vials 24 mL type 1 flint glass vials	Clear to opalescent, colorless to pale yellow liquid. May contain particles	Stores at 2 to 8 degrees Celsius (36 to 46 degrees Fahrenheit) and protected from light and freezing.

Please refer to FDA package insert for further details.
(https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/125554s058lbl.pdf)

Nivolumab will be given every four weeks at a dose of 480mg to be administered as a 30 minute IV infusion.

Subjects may be dosed every 28 days +/- 3 days from the previous dose of drug. There are no premedications recommended for nivolumab on the first cycle. Subjects should be carefully monitored for infusion reactions during nivolumab administration. If an acute infusion reaction is noted, subjects should be managed according to Protocol Section 6.1.

9.5 Avelumab Product Information

Product description and dosage form	Potency	Primary Packaging (volume)/Label type	Appearance	Storage condition (per label)
Avelumab Solution for Injection	200 mg/Vial (20 mg/mL)	10 mL type 1 flint glass vials	Clear to opalescent, colorless to pale yellow liquid. May contain particles	Stores at 2 to 8 degrees Celsius (36 to 46 degrees Fahrenheit) and protected from light and freezing.

Please refer to FDA package insert for further details. (https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/761049s006lbl.pdf)

Avelumab will be given every 2 weeks at a dose of 800 mg to be administered as a 60 minute IV infusion.

Subjects may be dosed every 14 days +/- 2 days from the previous dose of drug. Patients will need to be premedicated with acetaminophen and an antihistamine for the first 4 infusions and subsequently as needed. Subjects should be carefully monitored for infusion reactions during avelumab administration. If an acute infusion reaction is noted, subjects should be managed according to Protocol Section 6.1.

10.0 CORRELATIVE STUDIES

Please reference Section 1.4 for Background and Rationale for Correlative Studies

10.1 Blood Correlatives

At the time of imaging patients will also undergo blood draws for immunomodulatory cells. Whole blood (2 10 ml Sodium Heparin vacutainer tubes) will be collected for all time points by a member of the research team and delivered to the lab of Dr. Marcela Díaz-Montero (Cleveland Clinic Lerner Research Institute) for processing. Levels of cytokines associated with the suppressive function of MDSCs and Tregs (IL-1B, IL-10, IL-6, TGF-beta) and/or associated with anti-tumor activity of T cells (IFN- gamma, TNF-alpha) will be measured by ELISA in the plasma and correlated with levels of MDSC subtypes (PMN(granulocytic) (CD33+CD15+CD14- HLADR-), immature (CD33+CD15-CD14- HLADR-) and monocytic (CD33+CD14+CD15-HLADR-)) and Tregs (CD4+CD25+FOXP3+) by flow cytometry. Plasma will also be frozen and stored for future analyses.

10.2 Tissue Correlatives

Biopsies are recommended at specific time points to investigate the genomic and immunologic markers that are associated with response or resistance to therapy. Regarding biopsy timing, a biopsy is recommended at any time during cycle 1 (for PR and SD patients) and within 3 weeks of any other time period at which a PD or PR is

achieved in any patient (unless not feasible or unsafe per investigator discretion). Fresh biopsy specimens will be sent to the Lab of Dr. Marcela Diaz for nucleic acid isolation for gene expression analyses. In the event that archival tissue is only available nucleic acid will be isolated from formalin fixed tissue. A minimum of 3 unstained slides, up to 6 months prior to enrollment are allowed. Samples will be sent to the lab of Dr. C Marcela Diaz- Montero within 30 days of enrollment. Nucleic acid will be stored in a designated freezer at -80°C.

10.3 Address for tissue and blood specimen

Lerner Research

2111 E. 96th St.

[redacted]

Cleveland, OH 44106

Attention: [redacted]

Please provide advance notice by calling the lab at [redacted] or emailing [redacted]

11.0 STUDY PARAMETERS AND CALENDAR

	Screening (≤ 4 weeks prior to dosing)	Cycle 1 Day1 (+/- 3 days)[1] *	Cycle 2+ D1 (+/- 2 or 3 days) for patients on therapy and for patients re- starting therapy[2*]	Patients OFF therapy: every 6 weeks (+/- 3 days)[13]	Patients OFF therapy: Every 12 weeks (+/- 3 days)[13]	End of Treatment (+/- 3 days) [14]	Post Study follow up(+/- 3 days) [15]
Informed Consent	X						
ECOG PS, Weight (screening only), Vital Signs	X	X	X	X	X	X	
History/Physical[3]	X	X	X	X	X	X	
Adverse Events		X	X	X	X	X	X
Hematology[4]	X	X	X	X	X	X	
Chemistry[5]	X	X	X	X	X	X	
TSH, T4, T3[6]	X		X		X		
Autoimmune labs[7]	X						
Correlative Studies[8]	X		X		X		
CPI		X	X				
Tumor Imaging[9]	X		X		X	As clinically indicated	As clinically indicated
Brain CT or MRI[10]	As clinically indicated		As clinically indicated		X	As clinically indicated	As clinically indicated
Bone Scan[11]	As clinically indicated		As clinically indicated		X	As clinically indicated	As clinically indicated
Biopsy[12]	X						

*One Cycle is 14-28 days. Visit window +/- 3 days for Atezolizumab, Nivolumab, and Pembrolizumab. Visit window is +/- 2 days for Avelumab and Durvalumab.

1. Cycle 1 Day 1 Hematology, chemistry, autoimmune labs, and physical exam need not be repeated if done within 14 days
2. History, physical, AEs, Hematology, Chemistry to be done D1 (+/- 3 days) of every cycle
3. Baseline exam should be comprehensive. Subsequent physical exams can be targeted exams.

4. **Hematology**: CBC with differential, hemoglobin, hematocrit, platelets
5. **Blood chemistry:** sodium, potassium, chloride, bicarbonate, BUN, creatinine, albumin, total albumin, bicarbonate, AST, ALT, glucose, LDH (baseline only)
6. **TSH, T4, T3**: Screening, and on all imaging days, then as clinically indicated.
7. **Autoimmune labs** ANA by IFA screen, Anti-ENA, Anti-DNA DS, Rheumatoid factor, CCP antibody, ESR, CRP. These only need to be drawn if not drawn prior to initial treatment with CPI therapy.
8. **Correlative studies:** Correlative studies will be drawn with blood draws at biopsy, screening and prior to each imaging.
9. **Tumor imaging:** CT of the chest, abdomen, and pelvis (with contrast, if possible) to be performed to assess disease status at screening, and every 12 weeks from Cycle 1 Day 1. Tumor imaging should also be done whenever disease progression is suspected and as clinically indicated.
10. **Brain imaging** Brain CT or MRI scan to be performed as clinically indicated.
11. **Bone imaging:** Bone scan to be performed if clinically indicated.
12. **Biopsy** is recommended at any time during cycle 1 (for PR and SD patients) and within 3 weeks of any other time period at which a PD or PR is achieved in any patient (unless not feasible or unsafe per investigator discretion. Archival tissue up to 6 months prior to enrollment is acceptable in lieu of a cycle 1 biopsy
13. **OFF treatment** Patients will be seen every 12 weeks. The 6-week interim visit between scans will be done if clinically indicated. Labs during the 6-week interim visit should be as clinically indicated.
14. **End of treatment:** End of treatment visit is defined as the visit during which the patient will be removed from the study (even if not receiving drug at that visit.
15. **Post- study follow up** Patients will continue to be followed for at least 30 days after the last dose of CPI therapy or until new anti-cancer treatment is initiated, whichever comes first. Phone follow-up is sufficient.

12.0 MEASUREMENT OF EFFECT

Patients must have measurable disease at screening and will be evaluated for response on the basis of RECIST criteria version 1.1.[44] Tumor measurements using physical examination, spiral CT scan and/or MRI or other appropriate techniques deemed suitable by the investigator will be performed at screening within 28 days of patient registration and repeated per study calendar (Section 11.0) Scans can be done more frequently per MD discretion; these scans will be submitted on an unscheduled disease assessment.

13.0 DATA REPORTING / REGULATORY CONSIDERATIONS

13.1 Data Reporting

The Forte™ EDC and OnCore® databases will be utilized, as required by the Case Comprehensive Cancer Center and Cleveland Clinic, to provide data collection for both accrual entry and trial data management. Forte™ EDC and OnCore® are Clinical Trials Management Systems housed on secure servers. Access to data through Forte™ EDC and OnCore® is restricted by user accounts and assigned roles. Once logged into the Forte™

EDC or OnCore® system with a user ID and password, Forte™ EDC and OnCore® define roles for each user which limits access to appropriate data. User information and password can be obtained by contacting the OnCore® Administrator at OnCore-registration@case.edu for OnCore® access, and taussigoncore@ccf.org for Forte™ EDC access.

Forte™ EDC is designed with the capability for study setup, activation, tracking, reporting, data monitoring and review, and eligibility verification. When properly utilized, Forte™ EDC is 21 CFR 11 compliant. This study will utilize electronic Case Report Form completion in the Forte™ EDC database. A calendar of events and required forms are available in Forte™ EDC.

13.2 Regulatory Considerations

The study will be conducted in compliance with ICH guidelines and with all applicable federal (including 21 CFR parts 56 & 50), state or local laws.

13.2.1 Written Informed consent

Provision of written informed consent must be obtained prior to any study-related procedures. The Principal Investigator will ensure that the subject is given full and adequate oral and written information about the nature, purpose, possible risks and benefits of the study as well as the subject's financial responsibility. Subjects must also be notified that they are free to discontinue from the study at any time. The subject should be given the opportunity to ask questions and be allowed time to consider the information provided.

The original, signed written Informed Consent Form must be kept with the Research Chart in conformance with the institution's standard operating procedures. A copy of the signed written Informed Consent Form must be given to the subject. Additionally, documentation of the consenting process should be located in the research chart.

13.2.2 Subject Data Protection

In accordance with the Health Information Portability and Accountability Act (HIPAA), a subject must sign an authorization to release medical information to the sponsor and/or allow the sponsor, a regulatory authority, or Institutional Review Board access to subject's medical information that includes all hospital records relevant to the study, including subjects' medical history

13.2.3 Retention of records

The Principal Investigator of the Case Comprehensive Cancer Center supervises the retention of all documentation of adverse events, records of study drug receipt and dispensation, and all IRB correspondence for as long as needed to comply with local,

national and international regulations. No records will be destroyed until the Principal Investigator confirms destruction is permitted.

13.2.4 Audits and inspections

Authorized representatives of the sponsor, a regulatory authority, an Independent Ethics Committee (IEC) or an Institutional Review Board (IRB) may visit the site to perform audits or inspections, including source data verification. The purpose of an audit or inspection is to systematically and independently examine all study-related activities and documents to determine whether these activities were conducted, and data were recorded, analyzed, and accurately reported according to the protocol, Good Clinical Practice (GCP), guidelines of the International Conference on Harmonization (ICH), and any applicable regulatory requirements. For multi-center studies, participating sites must inform the sponsor-investigator of pending audits.

14.0 STATISTICAL CONSIDERATIONS

14.1 Sample Size Justification

In this phase II study, we will enroll at least 50 patients with advanced urothelial carcinoma who are refractory to first line therapy or who are cisplatin ineligible. Patients will be treated with CPI therapy for at least 20 weeks as per standard of care (SOC), at which time those with a tumor burden reduction of 10% or greater will suspend CPI therapy. If the number of patients with tumor burden reduction of ≥10% after 20 weeks is less than 20 patients, we will continue enrollment up to a maximum of 75 patients until the target sample size of 20 complete or partial responders has been reached. If we are not able to enroll 20 patients to the intermittent arm, after enrolling 75 patients, then we will deem the trial not feasible.

14.2 Safety considerations:

Table 1: Bayesian safety monitoring stopping rules. E.g. if we observed 4 or more PD by week 24 out of the first 6 patients, the trial will stop early.

Total number of patients	Number of patients with PD at 24 weeks
6	4-6
7 – 8	5-8
9 – 10	6-10
11 – 12	7-12
13 – 14	8-14
15 – 17	9-17
18-19	10-19

The primary safety endpoint is progression at 24 weeks post CPI suspension Based on Keynote 045, we expect approximately 40% of patients in this group to progress within one year,[45] we would consider a progression rate of 60% or more within the first 24 weeks of CPI suspension to be unacceptable. A higher than expected rate of rapid progression would indicate CPI suspension is not safe in this patient population. Accordingly, we have incorporated continuous safety monitoring stopping rules into our design to ensure patient safety (Table 1). Specifically, we will stop

the trial early and declare CPI suspension unsafe if there is strong evidence that CPI suspension results in higher than expected rates of progression at 24 weeks. We will use Bayesian safety monitoring and stop the trial early if Prob($PD_{24\,wk} > 0.4 \mid data) > 0.85$. We use a beta (0.4, 0.6) prior for the true rate of progression at 24 weeks, which corresponds to a prior expected progression rate of 0.4. Table 1 shows the corresponding stopping boundaries. If a patient progressed or died of disease, or lost to follow-up before 12 weeks, then the patient will be considered failure. Table 2 summarizes the operating characteristics.

Table 2. Summary of operating characteristics based on 10,000 simulations using monitoring rules specified in table 1. If the true PD rate at 24 weeks is 60%, the early stopping probability is 0.88.

Scenario	True PD rate at 24 weeks	Pr(Early Stoppping)	Average Sample Size	Average Number of PD Observed by Week 24
1	0.3	0.12	18.6	5.6
2	0.4	0.34	16.3	6.5
3	0.5	0.65	12.9	6.5
4	0.6	0.88	9.7	5.8

14.3 Efficacy:

Our primary efficacy endpoint is sustaining a response at 36 weeks following CPI suspension, and our primary objective is to estimate the proportion of patients able to sustain a response. We will estimate this proportion and construct an exact binomial 95% CI. With 20 patients, the half-width of the 95% CI won't exceed 0.23.

14.4 Analysis Plan

Summary statistics of toxicity and success status will be provided in frequencies and percentages. Toxicity and success rates will be estimated along with 95% CIs. Logistic regression model will be used to explore effects of patient and tumor characteristics on toxicity or success status. Survival endpoints will be estimated by Kaplan-Meier method and compared by log rank test. Cox proportional hazard model will be used to associate clinical factors and biomarkers with survival endpoints. Other statistical analyses will be carried out as appropriate.

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