Immune Checkpoint Inhibitors With or Without Propranolol Hydrochloride In Patients With Urothelial Carcinoma

WINSHIP PROTOCOL #: WINSHIP5200-20

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INVESTIGATIONAL PRODUCT (IP): [Propranolol]
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☒ **Study Exempt from IND Requirements per 21 CFR 312.2(b).**

REVISION HISTORY

Revision #	Version Date	Summary of Changes
Original	11/19/2020	
#1	6/1/2022	See SOC document

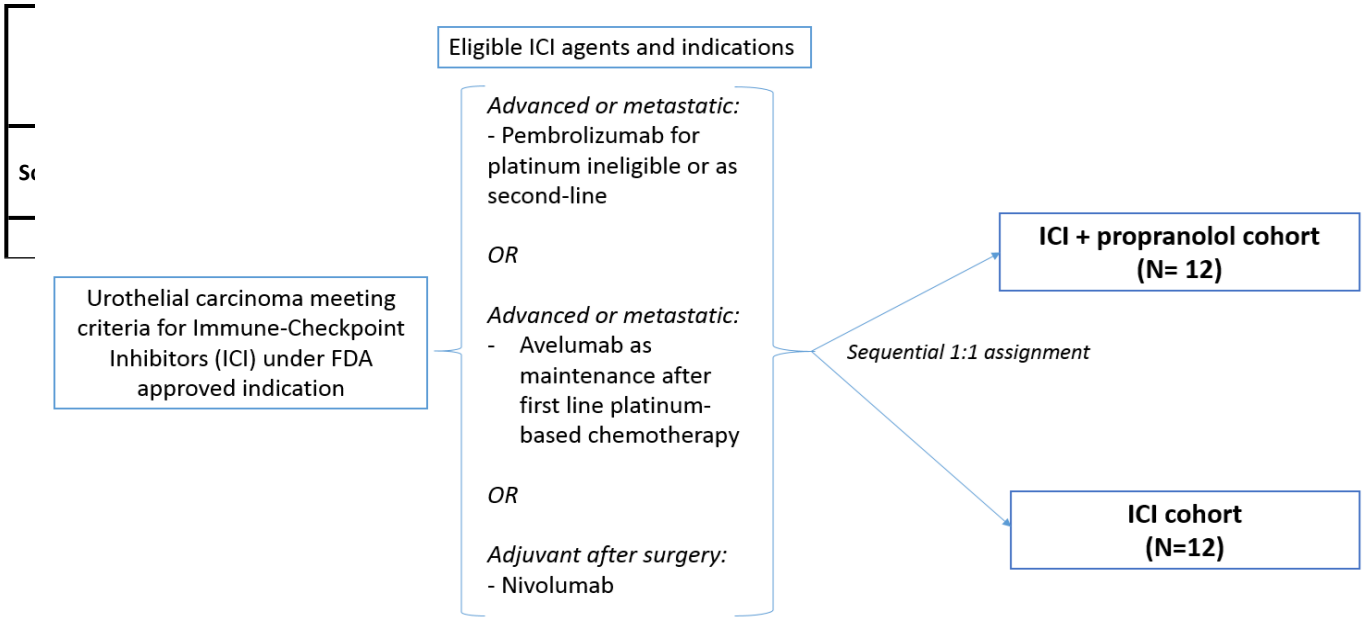
1. Study Summary

1.1 Synopsis

Title:	Immune Checkpoint Inhibitors With or Without Propranolol Hydrochloride In Patients With Urothelial Carcinoma
Study Description:	This research study is an open label study designed to evaluate the safety and translational correlative changes of the combination of propranolol hydrochloride and immune checkpoint inhibitors (ICI) in subjects with urothelial carcinoma.
Objectives:	**Primary Objectives:** To evaluate the safety of the combination of propranolol hydrochloride and immune checkpoint inhibitors in urothelial cancer. **Secondary Objective:** To describe response and survival outcomes for ICI plus or minus propranolol in patients with urothelial cancer To measure overall response rate (ORR) along with correlative changes in peripheral T-cell subsets, myeloid derived suppressor cells (MDSC), blood inflammatory markers and blood cytokines before and after treatment for patients receiving ICI plus propranolol vs. ICI alone. Available archival tissue will also be collected for tissue-based assays.
Endpoints:	**Primary Endpoint:** Safety: Incidence of adverse events according to the Common Terminology Criteria for Adverse Events (CTCAE) v5.0. **Secondary Endpoint:** Response: ORR per RECIST 1.1 (only for subjects receiving avelumab and pembrolizumab as ICI), profession free survival (PFS) and overall survival (OS). Correlatives: Changes in selected biomarkers in circulation before and after treatment for ICI plus propranolol vs. ICI alone.
Study Population:	The patient population consists of a total of 24 subjects ≥18 years of age with urothelial carcinoma (renal pelvis, ureter, bladder, or urethra), planned for treatment with nivolumab (adjuvant setting), pembrolizumab (advanced or metastatic), or avelumab (advanced or metastatic), under an FDA approved indications (listed below) at the genitourinary oncology clinics of Emory University's Winship Cancer Institute practice sites.
Phase:	Pilot study
Description of Sites / Facilities Enrolling:	Winship Cancer Institute of Emory University (Atlanta, GA)

Study Design:	Patients who meet eligibility criteria and consent for enrollment in the trial will be on one of the two study cohorts. Assignment to cohorts will be sequentially, in a 1:1 fashion, starting with the ICI plus propranolol cohort. The specific ICI that the subject would receive will be dependent on the clinical need and associated FDA approval. **ICI PLUS PROPRANOLOL COHORT:** 1. **Propranolol:** Participants will remain on propranolol 30mg twice daily for the duration of the trial unless unacceptable toxicity or withdrawal of consent. Patients who develop toxicity and stop propranolol will remain on trial for endpoint measurement. **PLUS** **Pembrolizumab:** Participants will receive 200mg IV on Day 1, every 3 weeks. Pembrolizumab would be continued for up to 2 years in the absence of disease progression or unacceptable toxicity. **OR** **Avelumab**: Participants will receive Avelumab at a dose of 10 mg per kilogram of body weight, IV on Day 1 every 2 weeks until disease progression or unacceptable toxicity. **OR** **Nivolumab**: Participants will receive Nivolumab (480mg) IV on every 4 weeks for up to 1 year or until disease recurrence or discontinuation from the trial. **ICI ALONE COHORT:** **Pembrolizumab:** Participants will receive 200mg IV on Day 1, every 3 weeks. Pembrolizumab would be continued for up to 2 years in the absence of disease progression or unacceptable toxicity. **OR** **Avelumab**: Participants will receive Avelumab at a dose of 10 mg per kilogram of body weight, IV on Day 1 every 2 weeks until disease progression or unacceptable toxicity **OR** **Nivolumab**: Participants will receive Nivolumab (480mg) IV on every 4 weeks for up to 1 year or until disease recurrence or discontinuation from the trial.
Study Duration:	Nivolumab +/- propranolol: up to 1 year or until disease recurrence or discontinuation from the trial Pembrolizumab +/- propranolol: up to 2 years or until disease progression or unacceptable toxicity Avelumab +/- propranolol: until disease progression or unacceptable toxicity

1.2 Schema



Dose of Propranolol
30mg oral BID

Dose of Pembrolizumab (advanced/metastatic setting)
200mg IV on Day 1, every 3 weeks

Dose of Avelumab (advanced/metastatic setting)
10mg/kg every 2 weeks

Dose of Nivolumab (adjuvant setting)
480mg IV every 4 weeks

1.3 Schedule of Assessments

	Screening	Treatment Cycle=42 days										Discontinuation	Safety Follow-up	Survival Follow-Up
Scheduling Window (Days):	-28 to -1	C1D1#	C1 D8	C1D15	C1D29	C2D1	C2D15	C2 D29	C3‡ D1	C3‡ D15	C3‡ D29	At time of Discont.	30 days post Discont.	Every 12 weeks
Informed Consent	X													
Inclusion/Exclusion Criteria	X													

	Screening	Treatment Cycle=42 days									Discontinuation	Safety Follow-up	Survival Follow-Up
Demographics and Medical History	X												
Prior and Con Med. Review	X	X			X	X	X	X	X	X	X		
ICC PLUS PROPRANOLOL COHORT: Propranolol Treatment (continuous, daily)*		X			X	X	X	X	X				
ICC ALONE COHORT*													
BOTH COHORT: PEMBROLIZUMAB (once every 3 weeks)		X			X	X	X	X	X				
Patient-reported Outcomes	X	X			X	X	X	X		X			
Survival Status	X	X				X		X		X	X	X	
Review Adverse Events		X			X	X	X	X	X	X	X	X	
Full Physical Examination	X	X											
Directed Physical Examination		X			X	X	X	X	X	X	X		
Vital Signs and Weight	X	X			X	X	X	X	X	X	X		
ECOG Performance Status	X	X			X	X	X	X	X	X	X		
Pregnancy Test – Urine or Serum β-HCG	X												
CBC with Differential	X	X			X	X	X	X	X	X	X		
Comprehensive Serum Chemistry Panel	X	X			X	X	X	X	X	X	X		
ECG†	X												
Stool sample for microbiome analysis (Only with at Screening and Cycle 3)§	X							X §					
Radiographic Tumor Assessment (every 12 weeks +/- 7 days)	X							X		X			
Archival Tissue Collection	X												
Correlative Blood Collection	X	X	X			X				X			

1.3.1 Subjects receiving pembrolizumab as ICI (ICI plus propranolol cohort *or* ICI alone cohort)

Screening procedures performed within 72 hours of Cycle 1 Day 1 (C1D1) do not need to be repeated on C1D1.

*Subjects are enrolled to either the ICI plus propranolol cohort or ICI alone cohort.

† At Screening, a single ECG will be obtained on which QTcF must be <450 ms. In case of clinically significant ECG abnormalities, including a QTcF value >450 ms, 2 additional 12-lead ECGs should be obtained over a brief period (e.g., 30 minutes) to confirm the finding. ‡ For C3 and all subsequent cycles.

§ Stool sample will be collected at baseline and at the first radiographic tumor assessment only

	Screening			Treatment Cycle=28 days							Discontiuation	Safety Follow-up	Survival Follow-Up
Demographics and Medical History	X												
Prior and Con Med. Review	X	X		X	X	X	X	X	X	X	X	X	
ICC PLUS PROPRANOLOL COHORT: Propranolol Treatment (continuous, daily)*		X	X	X	X	X	X	X	X	X			
Scheduling Window (Days):	-28 to -1		C1D1#		C1D8	C2D1		C2D15	C3D1	C4D1‡	At time of Discont.	30 days post Discont.	Every 12 weeks
ICC ALONE COHORT*													
Informed Consent	X												
BOTH COHORT: AVELUMAB (once every 2 weeks)		X		X	X	X	X	X	X	X	X		
Patient-reported Outcomes	X	X		X	X	X			X			X		
Survival Status	X	X				X			X			X	X	X
Review Adverse Events		X		X	X	X	X	X	X	X	X	X	X	X
Full Physical Examination	X	X												
Directed Physical Examination		X		X	X	X	X	X	X	X	X	X	X	
Vital Signs and Weight	X	X		X	X	X	X	X	X	X	X	X	X	
ECOG Performance Status	X	X		X	X	X	X	X	X	X	X	X	X	
Pregnancy Test – Urine or Serum β-HCG	X													
CBC with Differential	X	X		X	X	X	X	X	X	X	X	X	X	
Comprehensive Serum Chemistry Panel	X	X		X	X	X	X	X	X	X	X	X	X	
ECG†	X													
Stool sample for microbiome analysis (Only with Screening & Cycle 3)	X								X §					
Radiographic Tumor Assessment (every 12 weeks +/- 7 days)	X								X			X		
Archival Tissue Collection	X													
Correlative Blood Collection	X	X	X			X						X		

1.3.2 Subjects receiving avelumab as ICI (ICI plus propranolol cohort *or* ICI alone cohort)

Screening procedures performed within 72 hours of Cycle 1 Day 1 (C1D1) do not need to be repeated on C1D1.

*Subjects are enrolled to either the ICI plus propranolol cohort or ICI alone cohort.

† At Screening, a single ECG will be obtained on which QTcF must be <450 ms. In case of clinically significant ECG abnormalities, including a QTcF value >450 ms, 2 additional 12-lead ECGs should be obtained over a brief period (e.g., 30 minutes) to confirm the finding.

‡ For C3 and all subsequent cycles

§ Stool sample will be collected at baseline and at the first radiographic tumor assessment only

Inclusion/Exclusion Criteria	X									
Demographics and Medical History	X									
Prior and Con Med. Review	X	X		X		X	X	X	X	
ICC PLUS PROPRANOLOL COHORT: Propranolol Treatment (continuous, daily)*		X	X	X		X	X			
ICC ALONE COHORT*										
BOTH COHORT: NIVOLUMAB (once every 4 weeks)		X		X		X	X			
Patient-reported Outcomes	X	X		X		X	X	X		
Survival Status	X	X		X		X	X	X	X	X
Review Adverse Events		X		X		X	X	X	X	X
Full Physical Examination	X	X								
Directed Physical Examination		X		X		X	X	X	X	
Vital Signs and Weight	X	X		X		X	X	X	X	
ECOG Performance Status	X	X		X		X	X	X	X	
Pregnancy Test – Urine or Serum β-HCG	X									
CBC with Differential	X	X		X		X	X	X	X	
Comprehensive Serum Chemistry Panel	X	X		X		X	X	X	X	
ECG†	X									
Stool sample for microbiome analysis (Screening and Cycle 4 only)	X						X §			
Radiographic Tumor Assessment (every 12 weeks +/- 7 days)	X						X	X		
Archival Tissue Collection	X									
Correlative Blood Collection	X	X	X		X			X		

1.3.3 Schedule of Assessments for subjects receiving nivolumab (ICI plus propranolol cohort *or* ICI alone cohort)

Screening procedures performed within 72 hours of Cycle 1 Day 1 (C1D1) do not need to be repeated on C1D1.
*Subjects are enrolled to either the ICI plus propranolol cohort or ICI alone cohort.
† At Screening, a single ECG will be obtained on which QTcF must be <450 ms. In case of clinically significant ECG abnormalities, including a QTcF value >450 ms, 2 additional 12-lead ECGs should be obtained over a brief period (e.g., 30 minutes) to confirm the finding.
‡ For C4 and all subsequent cycles
§ Stool sample will be collected at baseline and at the first radiographic tumor assessment only

2. Objectives (and Endpoints)

OBJECTIVES	ENDPOINTS
Primary	

OBJECTIVES	ENDPOINTS
To safety as measured by incidence of adverse events assessed for ICI plus propranolol vs. ICI alone in patients with urothelial cancer	Safety: Incidence of adverse events according to the Common Terminology Criteria for Adverse Events (CTCAE) v5.0.
Secondary	
- To describe response to ICI plus or minus propranolol in metastatic urothelial cancer - To assess tissue-based assays in archival tissue and correlative changes in peripheral T-cell subsets, myeloid derived suppressor cells (MDSC), blood inflammatory markers and cytokines.	Response: ORR (for subjects receiving avelumab and pembrolizumab only), PFS, OS. Correlatives: Baseline tissue immune profile and changes in selected biomarkers and cell subsets before and after treatment.

3. Background

Propranolol is a commonly used non-selective beta-adrenergic receptor antagonist for the treatment chronic angina, cardiac arrhythmias, essential tremor, hypertension, and as prophylaxis for migraine headaches, among other indications. There are generic forms of propranolol available worldwide and it is listed on the WHO List of Essential Medicines. In recent years, there has been a mounting evidence of propranolol's potential anticancer properties. In-vitro and in-vivo data support prominent effects on limiting malignant cell proliferation, promoting tumor immune cells infiltration, blocking angiogenesis, and enhancing sensitivity to existing treatments[1]. The effects are seen among several tumor types. For instance, propranolol has anti-proliferative effects, attenuates migration of malignant cells, reduces VEGF and induces cell cycle arrest and apoptosis in both uveal melanoma and cutaneous melanoma in a dose-dependent manner[2]. In HER-2 amplified breast cancer where a strong association exists between trastuzumab-resistance and beta2 adrenergic signaling, propranolol inhibits the antagonist effect of catecholamine epinephrine to trastuzumab and can resensitize resistant cells both in vitro and in a xenograft model[3]. Interestingly, in a study of Irish women with breast cancer, the probability of breast cancer-specific mortality was lower in those women who used propranolol in the year prior to their breast cancer diagnosis compared to matched nonusers (HR = 0.19; 95% CI = 0.06 – 0.60)[4]. Further, the use of beta-blockers including propranolol is associated with reduced cancer-related psychological distress and better adjustment following a diagnosis of breast or colorectal cancer[5].

Immune checkpoint inhibition with PD-1/PD-L1 and CTLA-4 inhibitors has emerged as a bedrock of cancer therapy. However, those agents continue to have low response rates in the range of 10 to 25% and result in immune-related adverse events in some patients[6]. In fact, only a small subset of patients treated with immune checkpoint inhibitors derive long and durable responses. Drug combination approaches including drug repurposing are critically needed to allow a larger number of oncology patients to derive benefits from those treatments with fewer adverse events. Drug repurposing consists of finding new uses for already approved drugs that extend beyond the scope of the original medical indication. Advantages of this approach include the knowledge of the repurposed drug's safety profile, an expected lower development costs, and the reduced time frame for drug development. An example of approval using this approach include raloxifene to reduce the risk of hormone-receptor positive breast cancer in postmenopausal women at higher-than-average risk of developing breast cancer[7].

Urothelial carcinoma accounts for 90% of all bladder cancers in the United States. Less commonly, this histology can arise in the renal pelvis, ureter, or urethra. Each year, there are approximately 80,000 new cases and 18,000 deaths due to bladder cancer, with a median age of 69 years for men and 71 years for women[8]. The preferred frontline treatment of advanced or metastatic disease is cisplatin-based chemotherapy. However, over half of all patients cannot receive this treatment due to poor functional status, renal dysfunction, or other comorbidities.

Urothelial carcinoma is characterized by a high prevalence of tumor somatic mutations that is attributed to tobacco smoking and chronic environmental exposure of the urothelium to potential carcinogens that excreted in the urine. In turn, this is hypothesized to generate neoantigens recognized by activated antitumor T-cells and has led to the regulatory approval in this disease of immune checkpoint inhibitors (ICI) such as pembrolizumab, nivolumab, and avelumab.

The most common uses of ICI in urothelial cancer are:

i. Nivolumab as adjuvant treatment for high-risk muscle-invasive urothelial cancer after radical surgery. This is based on CheckMate 274 that demonstrated a disease-free survival benefit of adjuvant nivolumab vs. placebo [20.8 months (95% CI 16.5-27.6) vs 10.8 months (95% CI 8.3-13.9)][9], leading to the FDA approval in this setting.

ii. Avelumab as maintenance after platinum-based chemotherapy with no progression in advanced or metastatic urothelial cancer. The Javelin Bladder 100 trial showed a medial overall survival of 21.4 months vs. 14.3 months in patients received maintenance avelumab vs. best supportive care (Hazard ratio for death 0.69; 95% CI 0.56-0.86, P=0.001)[10], leading to the FDA approval in this setting.

iii. Pembrolizumab as frontline treatment in patients with advanced or metastatic urothelial cancer who are ineligible for platinum-based chemotherapy or as second line therapy in advanced or metastatic urothelial cancer. In the setting of recurrent or progressive disease after frontline platinum-based chemotherapy, the Keynote 045 phase III trials had significantly better ORR in the pembrolizumab arm (21.1%; 95% CI, 16.4-26.5) than in the chemotherapy group (11.4%; 95% CI, 7.9-15.8) (P=0.001) with fewer adverse events in the pembrolizumab arm (60.9%) compared with the chemotherapy arm (90.2%)[11].

Preclinical and clinical studies provide rationale for combining propranolol with ICI to enhance the anticancer activity of the latter. Beta adrenergic signaling significantly influences myeloid-derived suppressor cells (MDSC) frequency and survival in tumors and other tissues. It also modulates tumors expression of immunosuppressive molecules such as arginase-I and PD-L1[2,12]. Those effects can be mitigated by treatment with beta-adrenergic receptor antagonists, or enhanced by beta-AR agonists[13]. In a recent Phase II trial of breast cancer patients undergoing surgery with curative intent, perioperative treatment with propranolol resulted in favorable tumor immune infiltration of CD68+ macrophages and CD8+ cytotoxic T cells among patients who had clinical evidence of drug response (lower heart rate and blood pressure)[14].

We propose conducting a single-institution of ICI plus or minus propranolol in the treatment of urothelial cancer (adjuvant setting or advanced/metastatic setting) under an FDA-approved indications.

3.1 Clinical Experience

The combination of propranolol and ICI as planned in this trial has not been previously tested in urothelial carcinoma. In a retrospective analysis of 195 patients with metastatic melanoma treated with an immune-based

therapy, OS was significantly improved in patients receiving a non-selective beta-blocker compared to no-beta blocker[15]. This has led to an ongoing Phase Ib/II trial testing the combination of propranolol and pembrolizumab in metastatic melanoma (NCT03384836). Gandhi et al. recently reported the Phase I part of this trial. Nine patients with metastatic melanoma received pembrolizumab and increasing doses of propranolol in 10mg, 20mg, and 30mg BID escalation levels. No dose-limiting toxicities were reported. Rash, fatigue, and vitiligo were the most common side effects, with observed incidence of 44%. The objective response rate was a remarkable 78%. Propranolol 30mg BID was selected as the recommended phase 2 (RP2D) dose in addition to ICI based on safety, tolerability, and preliminary efficacy data[16].

The drugs are used separately for an extensive list of FDA-approved indications in oncology (ICI: metastatic melanoma, non-small cell lung cancer, urothelial cancer, among others) and cardiology (propranolol: hypertension, angina pectoris, atrial fibrillation, among others) with well documented toxicity profiles. Propranolol's usual dose range for most indications is 40mg to 320mg daily. The RP2D dosing of propranolol of 30mg BID in this trial is therefore on the lower end of what can be used in clinical practice. There are no contra-indications for the combined use of propranolol and pembrolizumab when this is routinely done for separate oncological and cardiac indications.

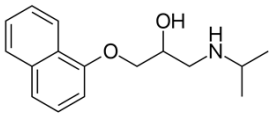
4. Study Intervention/Investigational Agent

4.1 Description

PROPRANOLOL

Propranolol hydrochloride (Inderal®) is a synthetic beta-adrenergic receptor blocking agent chemically described as 2-Propanol, 1-[(1-methylethyl)amino]-3-(1-naphthalenyloxy)-, hydrochloride,(±)-. Its molecular and structural formulae are:

C16H21NO2



Propranolol hydrochloride is a stable, white, crystalline solid which is readily soluble in water and ethanol. Its molecular weight is 295.80. It is available as 10 mg, 20 mg, 40 mg, 60 mg, and 80 mg tablets for oral administration.

Mechanism of Action

Propranolol is a nonselective beta-adrenergic receptor blocking agent possessing no other autonomic nervous system activity. It specifically competes with beta-adrenergic receptor agonist agents for available receptor sites. When access to beta-receptor sites is blocked by propranolol, the chronotropic, inotropic, and vasodilator responses to beta-adrenergic stimulation are decreased proportionately. At dosages greater than required for beta blockade, propranolol also exerts a quinidine-like or anesthetic-like membrane action, which affects the cardiac action potential. The significance of the membrane action in the treatment of arrhythmias is uncertain.

The mechanism of the antihypertensive effect of propranolol has not been established. Factors that may contribute to the antihypertensive action include: (1) decreased cardiac output, (2) inhibition of renin release by the kidneys, and (3) diminution of tonic sympathetic nerve outflow from vasomotor centers in the brain. Although total peripheral resistance may increase initially, it readjusts to or below the pretreatment level with

chronic use of propranolol. Effects of propranolol on plasma volume appear to be minor and somewhat variable.

In angina pectoris, propranolol generally reduces the oxygen requirement of the heart at any given level of effort by blocking the catecholamine-induced increases in the heart rate, systolic blood pressure, and the velocity and extent of myocardial contraction. Propranolol may increase oxygen requirements by increasing left ventricular fiber length, end diastolic pressure, and systolic ejection period. The net physiologic effect of beta-adrenergic blockade is usually advantageous and is manifested during exercise by delayed onset of pain and increased work capacity.

Propranolol exerts its antiarrhythmic effects in concentrations associated with beta-adrenergic blockade, and this appears to be its principal antiarrhythmic mechanism of action. In dosages greater than required for beta blockade, propranolol also exerts a quinidine-like or anesthetic-like membrane action, which affects the cardiac action potential. The significance of the membrane action in the treatment of arrhythmias is uncertain.

The mechanism of the antimigraine effect of propranolol has not been established. Beta-adrenergic receptors have been demonstrated in the pial vessels of the brain.

The specific mechanism of propranolol's anti-tremor effects has not been established, but beta-2 (noncardiac) receptors may be involved. A central effect is also possible. Clinical studies have demonstrated that Inderal is of benefit in exaggerated physiological and essential (familial) tremor.

Absorption: Propranolol is highly lipophilic and almost completely absorbed after oral administration. However, it undergoes high first-pass metabolism by the liver and on average, only about 25% of propranolol reaches the systemic circulation. Peak plasma concentrations occur about 1 to 4 hours after an oral dose. Administration of protein-rich foods increase the bioavailability of propranolol by about 50% with no change in time to peak concentration, plasma binding, half-life, or the amount of unchanged drug in the urine.
Refer to the package insert for complete details:
https://www.accessdata.fda.gov/drugsatfda_docs/label/2011/016418s080,016762s017,017683s008lbl.pdf

Pembrolizumab

Pembrolizumab is an IgG4 kappa immunoglobulin with an approximate molecular weight of 149 kDa. Pembrolizumab will be provided as a sterile, preservative-free, clear to slightly opalescent, colorless to slightly yellow solution that requires dilution for IV infusion.

- Pembrolizumab solution is provided in single-dose vials containing 100 mg/4 mL (25 mg/mL). Each 1 mL of solution contains 25 mg of pembrolizumab and is formulated in L-histidine (1.55 mg), polysorbate 80 (0.2 mg), sucrose (70 mg), and Water for Injection, USP.
- The Pharmacy Manual contains specific instructions for the preparation of the pembrolizumab infusion and administration of the infusion solution. An infusion of pembrolizumab in this study will require 2 vials of solution.

Pembrolizumab will be supplied in commercial packaging, which includes the package insert or patient information leaflet. Refer to the latest package insert for complete details:
https://www.merck.com/product/usa/pi_circulars/k/keytruda/keytruda_pi.pdf

Avelumab

Avelumab is a programmed death ligand1 (PD-L1) blocking antibody. Avelumab- is a human IgG1 lambda

monoclonal antibody produced in Chinese hamster ovary cells and has a molecular weight of approximately 147 kDa.

BAVENCIO (avelumab) Injection for intravenous use is a sterile, preservative-free, nonpyrogenic, clear, colorless to slightly yellow solution. Each single-dose vial contains 200 mg avelumab in 10 mL (20 mg/mL). Each mL contains 20 mg avelumab, D-mannitol (51 mg), glacial acetic acid (0.6 mg), polysorbate 20 (0.5 mg), sodium hydroxide (0.3 mg), and Water for Injection. The pH range of the solution is 5.0 – 5.6.
Refer to the latest package insert for complete details:
https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/761049s006lbl.pdf

Nivolumab
Nivolumab is a programmed death receptor-1 (PD-1) blocking antibody. Nivolumab is an IgG4 kappa immunoglobulin that has a calculated molecular mass of 146 kDa. It is expressed in a recombinant Chinese Hamster Ovary (CHO) cell line.

OPDIVO is a sterile, preservative-free, non-pyrogenic, clear to opalescent, colorless to pale-yellow liquid that may contain light (few) particles.

OPDIVO (nivolumab) injection for intravenous use is supplied in single-dose vials. Each mL of OPDIVO solution contains nivolumab 10 mg, mannitol (30 mg), pentetic acid (0.008 mg), polysorbate 80 (0.2 mg), sodium chloride (2.92 mg), sodium citrate dihydrate (5.88 mg), and water for injection, USP. May contain hydrochloric acid and/or sodium hydrozide to adjust pH to 6.

Refer to the latest package insert for complete details:
https://www.accessdata.fda.gov/drugsatfda_docs/label/2022/225554s112lbl.pdf

4.2 Drug/Device Handling
Clinical supplies must be stored in a secure, limited-access location under the storage conditions specified on the label. Receipt and dispensing of trial medication must be recorded by an authorized person at the trial site. Clinical supplies may not be used for any purpose other than that stated in the protocol.

Propranolol
Propranolol will be stored at controlled room temperature 20° to 25° C (68° to 77° F); excursions permitted to 15° to 30° C (59° to 86° F).

Dispense in a well-closed, light-resistant container as defined in the USP. Protect from light.
Use carton to protect contents from light.

Propranolol is claimed for IND exemption. It is already FDA-approved for many indications. Its addition to standard of care ICI in this study involves a relatively low dose (30mg BID) compared to its maximal dose in clinical use (up to 320mg daily) that is not expected to significantly increase the risk associated with propranolol. The investigation is not intended to be reported to FDA as a well-controlled study. Also, the investigation will be conducted in compliance with the requirements for IRB review and informed consent.

Pembrolizumab (Keytruda)
The product does not contain a preservative. Store reconstituted and diluted solution from the pembrolizumab 50 mg vial either:

- At room temperature for no more than 6 hours from the time of reconstitution. This includes room temperature storage of reconstituted vials, storage of the diluted solution, and the duration of infusion.
- Under refrigeration at 2°C to 8°C (36°F to 46°F) for no more than 24 hours from the time of reconstitution. If refrigerated, allow the diluted solution to come to room temperature prior to administration.

Store the diluted solution from the pembrolizumab 100 mg/4 mL vial either:

- At room temperature for no more than 6 hours from the time of dilution. This includes room temperature storage of the diluted solution, and the duration of infusion.
- Under refrigeration at 2°C to 8°C (36°F to 46°F) for no more than 24 hours from the time of dilution. If refrigerated, allow the diluted solution to come to room temperature prior to administration. Discard after 6 hours at room temperature or after 24 hours under refrigeration.

Do not freeze.

Avelumab (BAVENCIO)

Preparation

- Visually inspect vial for particulate matter and discoloration. BAVENCIO is a clear, colorless to slightly yellow solution. Discard vial if the solution is cloudy, discolored, or contains particulate matter.
- Withdraw the required volume of BAVENCIO from the vial(s) and inject it into a 250 mL infusion bag containing either 0.9% Sodium Chloride Injection or 0.45% Sodium Chloride injection.
- Gently invert the bag to mix the diluted solution and avoid foaming or excessive shearing.
- Inspect the solution to ensure it is clear, colorless, and free of visible particles.
- Discard any partially used or empty vials.

Storage of diluted BAVENCIO solution

Protect from light.

Store diluted BAVENCIO solution:

- At room temperature up to 77°F (25°C) for no more than 4 hours from the time of dilution. **Or**
- Under refrigeration at 36°F to 46°F (2°C to 8°C) for no more than 24 hours from the time of dilution. If refrigerated, allow the diluted solution to come to room temperature prior to administration.

Do not freeze or shake diluted solution.

Nivolumab (OPDIVO)

Visually inspect for particulate matter and discoloration. OPDIVO is a clear to opalescent, colorless to pale-yellow solution. Discard if cloudy, discolored, or contains extraneous particulate matter other than a few translucent-to-white, proteinaceous particles. Do not shake.

Preparation

- Withdraw the required volume of OPDIVO and transfer into an intravenous container.
- Dilute OPDIVO with either 0.9% Sodium Chloride Injection, USP or 5% Dextrose Injection, USP to prepare an infusion with a final concentration ranging from 1 mg/mL to 10 mg/mL. The total volume of infusion must not exceed 160 mL.
- For adult and pediatric patients with body weight ≥40 kg, do not exceed a total volume of infusion of 160 mL.
- Mix diluted solution by gentle inversion. Do not shake.

- Discard partially used vials or empty vials of OPDIVO.
- The product does not contain a preservative.
- After preparation, store the diluted solution either:
- At room temperature and room light for no more than 8 hours from the time of preparation to end of the infusion. Discard diluted solution if not used within 8 hours from the time of preparation; or
- Under refrigeration at 2°C to 8°C (36°F to 46°F) and protected from light for no more than 7 days from the time of preparation to end of infusion. Discard diluted solution if not used within 7 days from the time of preparation.

Do not freeze.

4.3 Accountability

The study drug provided for this study will be used only as directed in the study protocol. The Winship IDS (Investigational Drug Service) personnel will account for all study drugs. Drug accountability should be performed until the patient stops study treatment completely. Study site personnel will account for all study drugs received at the site.

Study drug supplies must be kept in an appropriate, secure locked area and stored in accordance with the conditions specified on the labels. The Investigator, pharmacist, or designee must maintain an accurate record of dispensing the study drug/s in a Drug Accountability Log.

The Drug Accountability Log may record specifics to study drug dispensation such as:

- Records of product delivery, inventory, temperature monitoring, destruction, and return.
- Dosages prepared, time prepared, doses dispensed.
- Doses and/or vials destroyed.
- The Drug Accountability Log may be reviewed by the monitor during site visits and at the completion of the study.

Drug accountability may be noted by the internal monitor during site visits and at the completion of the study. Patients will be asked to return all unused study treatment and packaging on a regular basis, at the end of the study or at the time of study treatment discontinuation.

The study drug supply will be disposed of per Winship's Investigational Drug Service (IDS) SOP. Compliance will be assessed by the investigator and/or study personnel at each patient visit and information provided by the patient and/or caregiver (collection of drug diary) will be captured in the Drug Accountability Form. This information must be captured in the source document at each patient visit. The patient might be requested to maintain a medication diary of each dose of medication. The medication diary (Appendix C) will be returned to clinic staff at the end of each cycle. Dose changes and interruptions of study drug must be specifically documented in the patient source documents and eCRF.

5. Procedures Involved

5.1 Study Design

This is a pilot study on safety and correlative translational markers of the combination of propranolol hydrochloride in combination with ICI in the treatment of urothelial cancer under an FDA-approved indication.

The trial plans to enroll 24 patients. The study is divided into a Screening period, Treatment period, End of Treatment (EOT) period, and Follow-up period.

During Screening period, patients will provide written informed consent to participate in the study before completing any protocol-specified procedures or evaluations not considered to be part of the patient's standard care.

Subjects will be assigned to either ICI + propranolol arm or the ICI (standard of care) arm sequentially. The first patient on the trial will be assigned to the ICI + propranolol arm. The specific ICI the subject would receive depends on the clinic need and would follow FDA-approved indications (i.e. nivolumab for high-risk urothelial bladder cancer after radical surgery, avelumab for advanced or metastatic disease as maintenance after platinum-based chemotherapy with no progression, or pembrolizumab for first line if ineligible for platinum-based chemotherapy or as subsequent line therapy). The specific ICI would not influence assignment to either arms. Procedures that were performed for standard of care prior to signing informed consent may be used for screening purposes (e.g., full physical exam) as long as the procedures were completed within the **28-day screening period.** After signing the ICF, patients will be evaluated for entry criteria during the screening period within 28 days before administration of study drug(s). Rescreening after screen failure will be allowed.

For subjects receiving Treatment duration will continue until unacceptable toxicity, death, disease progression per RECIST 1.1[17], Investigator's decision to discontinue treatment, the patient withdraws consent, lost to follow-up, or Institution decides to terminate the trial.

5.2 Dosing and Administration

Subjects receiving Pembrolizumab

Arm	Regimen Description					
	Agent	Premedications / Precautions	Dose	Route	Schedule	Cycle Length
ICI plus propranolol	Pembrolizumab	None	200 mg	IV infusion over 30 min	Q3W	42 days (6 weeks)
	Propranolol hydrochloride	None	30mg	Oral	BID, Continuous	
ICI Alone	Pembrolizumab	None	200mg	IV infusion over 30 min	Q3W	

Subjects receiving Avelumab

Arm	Regimen Description					
	Agent	Premedications / Precautions	Dose	Route	Schedule	Cycle Length
ICI plus propranolol	Avelumab	Acetaminophen and antihistamine prior to the first 4 infusions	10mg/kg	IV infusion over 60 min	Q2W	42 days (6 weeks)
	Propranolol hydrochloride	None	30mg	Oral	BID, Continuous	
ICI Alone	Avelumab	Acetaminophen and antihistamine prior to the first 4 infusions	10mg/kg	IV infusion over 60 min	Q2W	

Subjects receiving Nivolumab

Arm	Regimen Description					
	Agent	Premedications / Precautions	Dose	Route	Schedule	Cycle Length
ICI plus propranolol	Nivolumab	None	480mg	IV infusion over 30 min	Q4W	28 days (4 weeks)
	Propranolol hydrochloride	None	30mg	Oral	BID, Continuous	
ICI Alone	Nivolumab	None	480mg	IV infusion over 30 min	Q4W	

5.3 Dose Modification

The investigator will decide whether any AE that occurs is related to either or both drugs and determine whether dose modification or discontinuation of one or both drugs is required per the guidance below.

ICI (Pembrolizumab, Avelumab, and Nivolumab)

No dose reductions of ICI are recommended. Withhold or discontinue the drug to manage Adverse reactions as described in **Table 1**. Any infusion or hypersensitivity reactions occurring during the infusion of the pembrolizumab are not considered dose-related and therefore will NOT be considered to be an adverse event.

Table 1: Dose Modification for Adverse Events (AE) Associated with **ICI (Pembrolizumab, Avelumab, and Nivolumab):**

General instructions:

1. Corticosteroid taper should be initiated upon AE improving to Grade 1 or less and continue to taper over at least 4 weeks.

2. For situations where ICI has been withheld, ICI can be resumed after AE has been reduced to Grade 1 or 0 and corticosteroid has been tapered. ICI should be permanently discontinued if AE does not resolve within 12 weeks of last dose or corticosteroids cannot be reduced to ≤10 mg prednisone or equivalent per day within 12 weeks.

3. For severe and life-threatening AEs, IV corticosteroid should be initiated first followed by oral steroid. Other immunosuppressive treatment should be initiated if AEs cannot be controlled by corticosteroids.

Immune-related AEs	**Toxicity grade or conditions (CTCAEv5.0)**	**Action taken to pembrolizumab**	**irAE management with corticosteroid and/or other therapies**	**Monitor and follow-up**
Pneumonitis	Grade 2	Withhold	• Administer corticosteroids (initial dose of 1-2 mg/kg prednisone or equivalent) followed by taper	• Monitor participants for signs and symptoms of pneumonitis • Evaluate participants with suspected pneumonitis with radiographic imaging and initiate corticosteroid treatment • Add prophylactic antibiotics for opportunistic infections
	Grade 3 or 4, or recurrent Grade 2	Permanently discontinue		
Diarrhea / Colitis	Grade 2 or 3	Withhold	• Administer corticosteroids (initial dose of 1-2 mg/kg prednisone or equivalent) followed by taper	• Monitor participants for signs and symptoms of enterocolitis (ie, diarrhea, abdominal pain, blood or mucus in stool with or without fever) and of bowel perforation (ie, peritoneal signs and ileus). • Participants with ≥ Grade 2 diarrhea suspecting colitis should consider GI consultation and performing endoscopy to rule out colitis. • Participants with diarrhea/colitis should be advised to drink liberal quantities of clear fluids. If sufficient oral fluid intake is not feasible, fluid and electrolytes should be substituted via IV infusion.
	Grade 4	Permanently discontinue		
AST / ALT elevation or Increased bilirubin	Grade 2	Withhold	• Administer corticosteroids (initial dose of 0.5-1 mg/kg prednisone or equivalent) followed by taper	• Monitor with liver function tests (consider weekly or more frequently until liver enzyme value returned to baseline or is stable
	Grade 3 or 4	Permanently discontinue	• Administer corticosteroids (initial dose of 1-2 mg/kg prednisone or equivalent) followed by taper	

Type 1 diabetes mellitus (T1DM) or hyperglycemia	Newly onset T1DM or Grade 3 or 4 hyperglycemia associated with evidence of β-cell failure	Withhold	• Initiate insulin replacement therapy for participants with T1DM • Administer anti-hyperglycemic in participants with hyperglycemia	• Monitor participants for hyperglycemia or other signs and symptoms of diabetes.
Hypophysitis	Grade 2	Withhold	• Administer corticosteroids and initiate hormonal replacements as clinically indicated.	• Monitor for signs and symptoms of hypophysitis (including hypopituitarism and adrenal insufficiency)
	Grade 3 or 4	Withhold or permanently discontinue[1]		
Hyperthyroidism	Grade 2	Continue	• Treat with non-selective beta-blockers (eg, propranolol) or thionamides as appropriate	• Monitor for signs and symptoms of thyroid disorders.
	Grade 3 or 4	Withhold or permanently discontinue[i]		
Hypothyroidism	Grade 2-4	Continue	• Initiate thyroid replacement hormones (e.g., levothyroxine or liothyroinine) per standard of care	• Monitor for signs and symptoms of thyroid disorders.
Nephritis and Renal dysfunction	Grade 2	Withhold	• Administer corticosteroids (prednisone 1-2 mg/kg or equivalent) followed by taper.	• Monitor changes of renal function
	Grade 3 or 4	Permanently discontinue		
Myocarditis	Grade 1 or 2	Withhold	• Based on severity of AE administer corticosteroids	• Ensure adequate evaluation to confirm etiology and/or exclude other causes
	Grade 3 or 4	Permanently discontinue		
All other immune-related AEs	Intolerable/ persistent Grade 2	Withhold	• Based on type and severity of AE administer corticosteroids	• Ensure adequate evaluation to confirm etiology and/or exclude other causes
	Grade 3	Withhold or discontinue based on the type of event. Events that require discontinuation include and not limited to: Gullain-Barre		

		Syndrome, encephalitis		
	Grade 4 or recurrent Grade 3	Permanently discontinue		
i. Withhold or permanently discontinue ICI is at the discretion of the investigator or treating physician. **NOTE:** For participants with Grade 3 or 4 immune-related endocrinopathy where withhold of ICI is required, ICI may be resumed when AE resolves to ≤ Grade 2 and is controlled with hormonal replacement therapy or achieved metabolic control (in case of T1DM).				

Propranolol

No dose reductions of Propranolol are recommended (**Table 2**).

Table 2: Dose Modification for Adverse Events (AE) Associated with **Propranolol:**

Grade 1	Continue, monitor closely
Grade 2	Withhold for 3 days, monitor closely.
Grade 3	Permanently discontinue
Grade 4	Permanently discontinue

Propranolol will be permanently discontinued if Grade 3 or more cardiac (**Table 3**) and non-cardiac adverse events attributed to propranolol as defined by CTCAE Version 5. The full list of adverse events that have been attributed to Propranolol appears in the protocol section *14. Risk to Participants*.

Table 3: Cardiac Adverse Events Associated with **Propranolol**

	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Sinus bradycardia*	Asymptomatic, intervention not indicated	Symptomatic, intervention not indicated; change in medication initiated	Symptomatic, intervention indicated	Life-threatening consequences; urgent intervention indicated
Congestive Heart Failure	Asymptomatic with laboratory (e.g., BNP [B-Natriuretic Peptide]) or cardiac imaging abnormalities	Symptoms with moderate activity or exertion	Symptoms at rest or with minimal activity or exertion; hospitalization; new onset of symptoms	Life-threatening consequences; urgent intervention indicated (e.g., continuous IV therapy or mechanical
Hypotension†	Asymptomatic, intervention not indicated	Non-urgent medical intervention indicated	Medical intervention indicated; hospitalization indicated	Life-threatening consequences and urgent intervention indicated

Vascular disorders - Other, specify	Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated	Moderate; minimal, local or noninvasive intervention indicated; limiting age appropriate instrumental ADL	Severe or medically significant but not immediately life threatening; hospitalization or prolongation of existing hospitalization indicated; limiting self-care ADL	Life-threatening consequences; urgent intervention indicated

* CTCAE v5.0 definition: A disorder characterized by a dysrhythmia with a heart rate less than 60 beats per minute that originates in the sinus node.
†CTCAE v5.0 definition: A disorder characterized by a blood pressure that is below the normal expected for an individual in a given environment.

5.4 Concomitant medication

Medications or vaccinations specifically prohibited in the exclusion criteria are not allowed during the ongoing trial. If there is a clinical indication for one of these or other medications or vaccinations specifically prohibited during the trial, discontinuation from trial therapy or vaccination may be required.

Propranolol

Caution should be exercised when Propranolol is administered with drugs that have an effect on CYP2D6, 1A2, or 2C19 metabolic pathways. Co-administration of such drugs with propranolol may lead to clinically relevant drug interactions and changes on its efficacy and/or toxicity (see Drug Interactions in PHARMACOKINETICS AND DRUG METABOLISM).

Cardiovascular Drugs

- Antiarrhythmics
  - Propafenone has negative inotropic and beta-blocking properties that can be additive to those of propranolol.
  - Quinidine increases the concentration of propranolol and produces greater degrees of clinical beta-blockade and may cause postural hypotension.
  - Amiodarone is an antiarrhythmic agent with negative chronotropic properties that may be additive to those seen with β-blockers such as propranolol.
  - The clearance of lidocaine is reduced with administration of propranolol. Lidocaine toxicity has been reported following co-administration with propranolol.
  - Caution should be exercised when administering Inderal with drugs that slow A-V nodal conduction, e.g. digitalis, lidocaine and calcium channel blockers.

- Digitalis Glycosides
  - Both digitalis glycosides and beta-blockers slow atrioventricular conduction and decrease heart rate. Concomitant use can increase the risk of bradycardia.

- Calcium Channel Blockers
  - Caution should be exercised when patients receiving a beta blocker are administered a calcium channel-blocking drug with negative inotropic and/or chronotropic effects. Both agents may depress myocardial contractility or atrioventricular conduction.
  - There have been reports of significant bradycardia, heart failure, and cardiovascular collapse with concurrent use of verapamil and beta-blockers.
  - Co-administration of propranolol and diltiazem in patients with cardiac disease has been associated with bradycardia, hypotension, high-degree heart block, and heart failure.

- ACE Inhibitors
  - When combined with beta-blockers, ACE inhibitors can cause hypotension, particularly in the setting of acute myocardial infarction.
  - The antihypertensive effects of clonidine may be antagonized by beta-blockers. Propranolol should be administered cautiously to patients withdrawing from clonidine.
- Alpha Blockers
  - Prazosin has been associated with prolongation of first dose hypotension in the presence of beta-blockers.
  - Postural hypotension has been reported in patients taking both beta-blockers and terazosin or doxazosin.
- Reserpine
  - Patients receiving catecholamine-depleting drugs, such as reserpine, should be closely observed for excessive reduction of resting sympathetic nervous activity, which may result in hypotension, marked bradycardia, vertigo, syncopal attacks, or orthostatic hypotension.
- Inotropic Agents
  - Patients on long-term therapy with propranolol may experience uncontrolled hypertension if administered epinephrine as a consequence of unopposed alpha-receptor stimulation.
  - Epinephrine is therefore not indicated in the treatment of propranolol overdose (see OVERDOSAGE).
- Isoproterenol and Dobutamine
  - Propranolol is a competitive inhibitor of beta-receptor agonists, and its effects can be reversed by administration of such agents, e.g., dobutamine or isoproterenol. Also, propranolol may reduce sensitivity to dobutamine stress echocardiography in patients undergoing evaluation for myocardial ischemia.

Non-Cardiovascular Drugs

  - Nonsteroidal anti-inflammatory drugs (NSAIDS) have been reported to blunt the antihypertensive effect of beta-adrenoreceptor blocking agents.
  - Administration of indomethacin with propranolol may reduce the efficacy of propranolol in reducing blood pressure and heart rate.
- Antidepressants
  - The hypotensive effects of MAO inhibitors or tricyclic antidepressants may be exacerbated when administered with beta-blockers by interfering with the beta blocking activity of propranolol.
- Anesthetic Agents
  - Methoxyflurane and trichloroethylene may depress myocardial contractility when administered with propranolol.
- Warfarin
  - Propranolol when administered with warfarin increases the concentration of warfarin. Prothrombin time, therefore, should be monitored.

Neuroleptic Drugs

  - Hypotension and cardiac arrest have been reported with the concomitant use of propranolol and haloperidol.
- Thyroxine
  - Thyroxine may result in a lower than expected T3 concentration when used concomitantly with propranolol.
- Alcohol
  - Alcohol, when used concomitantly with propranolol, may increase plasma levels of propranolol.

ICI (Pembrolizumab, Avelumab, and Nivolumab)

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

- Antineoplastic systemic chemotherapy or biological therapy
- Immunotherapy not specified in this protocol
- Chemotherapy not specified in this protocol
- Investigational agents other than ICI/propranolol
- Radiation therapy
    - Note: Radiation therapy to a symptomatic solitary lesion or to the brain may be allowed at the investigator's discretion.
- Live vaccines within 30 days prior to the first dose of study treatment and while participating in the study. Examples of live vaccines include, but are not limited to, the following: measles, mumps, rubella, varicella/zoster, yellow fever, rabies, BCG, and typhoid vaccine. Seasonal influenza vaccines for injection are generally killed virus vaccines and are allowed; however, intranasal influenza vaccines (eg, FluMist®) are live attenuated vaccines and are not allowed.
- Systemic glucocorticoids for any purpose other than to modulate symptoms from an event of clinical interest of suspected immunologic etiology. The use of physiologic doses of corticosteroids may be approved after consultation with the Sponsor.

Participants who, in the assessment by the investigator, require the use of any of the aforementioned treatments for clinical management should be removed from the study. All treatments that the Investigator considers necessary for a participant's welfare may be administered at the discretion of the Investigator in keeping with the community standards of medical care.

Medications or vaccinations specifically prohibited in the exclusion criteria are not allowed during the ongoing study. If there is a clinical indication for any medication or vaccination specifically prohibited during the study, discontinuation from study therapy or vaccination may be required. The final decision on any supportive therapy or vaccination rests with the investigator and/or the participant's primary physician. However, the decision to continue the participant on study treatment requires the mutual agreement of the Investigator, the Sponsor and the participant. There are no prohibited therapies during the Post-Treatment Follow-up Phase.

5.5 Study Procedures

Before study entry, throughout the study, and following study drug discontinuation, various clinical and diagnostic laboratory evaluations are outlined. The purpose of obtaining these detailed measurements is to ensure adequate **safety and tolerability assessments**. Clinical evaluations and laboratory studies may be repeated more frequently if clinically indicated. The Schedules of Assessments during the screening and treatment period is provided following the Protocol Synopsis.

Screening Phase

Screening procedures will be performed up to 28 days prior to enrollment and initiation of radiation therapy as applicable, except for baseline imaging (up to 28 days allowed) unless otherwise specified. All subjects must first read, understand, and sign the IRB-approved ICF before any study-specific screening procedures are performed. After signing the ICF, completing all screening procedures, and being deemed eligible for entry, subjects will be enrolled in the study. Procedures that are performed prior to the signing of the ICF and are considered standard of care may be used as screening assessments if they fall within the screening window.

The following procedures will be performed during the **Screening Visit**:

- Informed Consent
- Review of eligibility criteria
- Medical history (prior history of cardiac disease will be evaluated) and demographics
- Complete physical exam
- ECOG Performance Status
- Patient-reported outcomes
- Vitals signs, weight and height
- 12-lead ECG
- Review of prior/concomitant medications
- Imaging by CT/MRI
- Archival tumor tissue collection
- Blood collection for research
- Clinical laboratory tests for:
  - Hematology
  - Clinical chemistry
  - Creatinine Clearance
  - Serum or urine pregnancy test (for women of childbearing potential)
  - Stool sample for microbiome analysis

Treatment Phase

Procedures to be conducted during the treatment phase of the study are presented in the Schedule of Assessments Screening procedures performed within 72 hours of Cycle 1 Day 1 (C1D1) do not need to be repeated on C1D1.

- Brief medical history
- Symptom-directed physical exam
- ECOG Performance Status
- Patient-reported outcomes
- Vitals signs, weight
- 12-lead ECG as clinically indicated
- Review of prior/concomitant medications
- Review of Adverse events
- Tumor imaging (every 12 weeks)
- Blood collection for research
- Clinical laboratory tests for:
  - Hematology
  - Clinical chemistry
  - Stool sample for microbiome analysis

End of Treatment

End of treatment is defined as the last planned dosing visit within the dosing period. For subjects who discontinue drug treatment, end of treatment is considered the last visit where the decision is made to discontinue treatment. All required procedures may be completed within ± **7 days** of the end of treatment visit. Repeat disease assessment is not required if performed within 28 days prior to the end of treatment visit.
Assessments for subjects who have completed treatment and achieved disease control or have discontinued treatment due to toxicity in the absence of confirmed progressive disease are provided in the Schedule of Event (Section1.3).

5.6 Description of Study Procedures

Medical history

Findings from medical history (obtained at screening) and physical examination shall be given a baseline grade according to the procedure for AEs. All patients will be screened for prior history of cardiac disease that raise the risk of complications by the medical oncologist when the trial information is presented.

Increases in severity of pre-existing conditions during the study will be considered AEs, with resolution occurring when the grade returns to the pre-study grade or below.

Physical examination

Physical examinations should be conducted according to the Schedule of Events. Full physical examinations should be conducted at screening/baseline, and EOT (evaluate all major organ systems, including the following categories: general, head, eyes, ears, mouth/throat, neck, heart, lungs, abdomen, lymph nodes, joints, extremities, integumentary, neurologic, and psychiatric). Other examinations during treatment may be focused, at the discretion of the Investigator, to identify changes from baseline or evaluate changes based on the patient's clinical symptoms. Weight is to be recorded at each visit, height at screening/baseline visit only.

Vital signs

Vital signs (blood pressure [BP], pulse, temperature, and respiration rate) will be evaluated according to the assessment schedules. Body weight is also recorded along with vital signs.

On infusion days, patients receiving treatment will be monitored during and after infusion of study drug. Additional monitoring with assessment of vital signs is at the discretion of the Investigator per standard clinical practice or as clinically indicated.

Patient-reported outcomes

The National Comprehensive Cancer Network FACT Bladder Symptom Index (NFBlSI-18) is a tool that allows measuring bladder cancer-specific symptoms in patients with advanced or metastatic disease. The tool was developed through qualitative assessment of the most important symptoms as perceived by patients and oncologists [18]. The score includes 18 questions in three subscale scores (i.e. disease-related symptoms, treatment side effects, and general function/well-being) and a summary score. A 5-point Likert scale ranging from 0 = 'not at all' to 4 = 'very much' in the preceding 7 days is used. The Manual of Functional Assessment of Chronic Illness Therapy (FACIT) Measurement System is employed to calculate the subscale and summary scores [19].

Participants will be asked to fill out the assessment tool in paper form and return them to the clinical trial team (Appendix D). The dates of Schedule of Assessments are shown in the Schedule of Assessments section.

Electrocardiograms

Resting 12-lead ECGs will be recorded at screening and as clinically indicated throughout the study. ECGs should be obtained after the patient has been in a supine position for 5 minutes and recorded while the patient remains in that position.
At Screening, a single ECG will be obtained on which QTcF must be <450 ms.

In case of clinically significant ECG abnormalities, including a QTcF value >450 ms, 2 additional 12-lead ECGs should be obtained over a brief period (e.g., 30 minutes) to confirm the finding.
The Investigator or qualified Sub-Investigator will review all ECG interpretations and interval duration measurements for clinical significance. Any ECG interpretation deemed to be clinically significant in the treatment phase will be reported as an AE.

Tumor and Radiographic Assessments

Tumor assessments for all patients will be performed at Screening and every 12 weeks (± 3 days) until the patient withdraws consent or starts a new antineoplastic regimen. Assessments will become less frequent during the long-term follow-up period. Tumor response or recurrence will be evaluated using RECIST 1.1[17].

Radiographic assessments (chest/abdomen/pelvis, and other known affected anatomical areas) are required for all patients for tumor measurements. Additional scan assessments may be collected based on clinical symptoms, as appropriate. Documented tumor measurements are required using CT scans, MRI, physical examination, and/or digital photography, as appropriate. Any imaging used to assess disease at any time point will be submitted for an independent radiology review. The same method of assessment (CT or MRI and/or digital photography) and the same technique for acquisition of images must be used for all study assessments (contrast must be used unless medically contraindicated). Baseline imaging should be done at the same institution/facility which will be used to measure response during the patient's participation in the study. Radiographic assessments and efficacy analyses will be conducted by the Investigator site as well as the independent radiology review committee.

Clinical laboratory tests

The following clinical laboratory tests will be performed (see the Schedule of Assessments)

- Hematology and Clinical Chemistry
- Pregnancy test (female subjects of childbearing potential only)
- Stool sample for microbiome analysis

6. Data and Specimen Banking

Tumor Tissue Collection

Tumor tissue will be collected prior to trial enrollment and allotment in the form of archival tissue. Tissue will be handled as follows:

- RNAlater for RNA stabilization and tissue storage
- Formalin-fixed paraffin-embedded (FFPE) block with one cut H&E stained slide
- Liquid nitrogen frozen tissue in cryo-preservation vials

All collected tissues are stabilized and stored in -80°C freezers (RNAlater stabilized, OCT embedded, short term storage) or the vapor phase of a liquid nitrogen freezer (long term storage) in single use aliquots. All FFPE tissue blocks are stored in a climate-controlled storage room that is temperature (less than 27ºC) and humidity controlled.

Tissue will be evaluated for assessment of mutations and/or immune markers including PD-1/PD-L1 and other relevant biomarkers (e.g. tumor infiltrating lymphocytes, T- cell repertoire, RNA signature profiles). When sufficient quantities of fresh tissue are available, it will also be dissociated, and flow cytometry will be used to

determine the phenotypic characteristics of cell populations in the tumor microenvironment. Tissue will be preserved for future exploratory studies including genomic profiling.

Correlative Studies Blood Sampling

Correlative peripheral blood samples will be collected prior to study drug allotment, on [(Cycle 1 Day 1, Cycle 1 Day 8, Cycle 2 Day 1 for subjects receiving avelumab or pembrolizumab as ICI) or (Cycle 1 Day 1, Cycle 1 Day 8, Cycle 2 Day 15 for subjects receiving nivolumab)]and in the post-treatment period as expanded in the Trial Flow Chart. Approximately 60 mL of peripheral blood will be collected at each time point. The samples will be stored in -80°C freezers until analysis. Stool sample will be collected at baseline, and at the time of the first restaging radiographic scan. Analysis may include but is not limited to:

- Circulating tumor DNA (ctDNA) to explore genetic alterations that are present are baseline and/or emerge during treatment
- Analysis of peripheral blood mononuclear cells (PBMCs) to assess for phenotypic/functional changes in T-cells or myeloid markers during and after treatment
- Nuclear acid analysis for gene expression profiling
- Stool sample for microbiome analysis

Shipping and handling instructions

After appropriate processing, the blood samples, tissue blocks, slides or frozen tissue samples, and stool samples will be sent: Kissick Laboratory, 1462 Clifton Rd, Room 420, Atlanta, Georgia, 30322

Data and specimens from this study may be useful for other research being done by investigators at Emory or elsewhere. To help further science, Investigators may provide de-identified data and/or specimens to other researchers. Any information that could identify participants will not be included. If data or specimens are labeled with study ID, we will not allow other investigators to link that ID to identifiable information.

Samples and data collected under this protocol may be used to study urothelial carcinoma. Access to stored samples will be limited to IRB-approved investigators. Samples and data will be stored using codes assigned by the investigators or their designees. Data will be kept in password-protected computers. Only investigators (or their designees) will have access to the samples and data.

All stored samples will be maintained in the laboratory to which it was sent initially for analysis. Study participants who request destruction of samples will be notified of compliance with such request and all supporting details will be maintained for tracking.

The results of some study tests and procedures will be used only for research purposes and will not be placed in subject's medical record. For this study, those items include research blood collection.

7. Sharing of Results with Participants

In general, study staff will not provide any individual results to subjects (e.g. outcome trial results or results from subject's samples studies). If something of urgent medical importance to the participating subjects will be found, the PI (or co-Is) will inform the subject, although we expect that this will be a very rare occurrence. Samples and data will only be used for research.

8. Study Timelines

8.1 Duration of therapy

In the absence of treatment delays due to adverse event(s), patients will be treated until any one of the following:

- Tumor progression per RECIST 1.1 for patients receiving avelumab; tumor progression per RECIST 1.1 pembrolizumab or completion of 2 years of therapy (whichever is first); tumor progression per RECIST 1.1 or completion of 1 year of therapy for patients receiving nivolumab (whichever is first)
- Death
- Unacceptable toxicity
- Symptomatic deterioration
- Investigator's decision to discontinue treatment
- Patient decision to discontinue treatment
- Patient withdraws consent
- Lost to follow up

In the event of a patient's withdrawal, the Investigator will make every effort to complete the End of Treatment procedures specified in the Schedule of Events.

8.2 Duration of follow-up

Patients will be followed for approximately 28 days (**Safety Follow-up**) after the last dose of study drug or before initiation of new antineoplastic or investigational therapy whichever occurs first. Patients removed from study for unacceptable adverse event(s) will be followed until resolution or stabilization of the adverse event.
Long-term follow-up should continue until the patient's withdrawal of consent or loss to follow up, death, or study termination for a duration of up to two years.

Patient records may be reviewed until death to assess progression and survival. Survival information may be collected by clinic visit, email, or telephone after ending protocol treatment and until the study is terminated, the patient dies, or the patient is lost to follow-up.

A participant will be considered lost to follow-up if he or she fails to return for three scheduled visits and is unable to be contacted by the study site staff after three attempts at contact by phone.
The following actions must be taken if a participant fails to return to the clinic for a required study visit:
The site will attempt to contact the participant and reschedule the missed visit and counsel the participant on the importance of maintaining the assigned visit schedule and ascertain if the participant wishes to and/or should continue in the study.

Patients removed from study for unacceptable adverse event(s) will be followed until resolution or stabilization of the adverse event.

Patients who have not initiated a new antineoplastic regimen will have the following assessments:

- Radiologic tumor assessments every 12 weeks (± 7 days) for up to two years as part of the trial
- In case of a clinically significant AE, patient will be followed for safety until resolution or permanent sequelae of all toxicities attributable to study drug(s). If the patient discontinues study drug for a clinically significant AE, the patient will be followed until resolution of the AE or the event is considered to be stable and/or chronic.

9. Inclusion and Exclusion Criteria

Inclusion Criteria

1. Male or Female
2. Age ≥18 years.
3. ECOG performance status ≤2 (Karnofsky ≥60%, see Appendix A).
4. Patients must have histologically confirmed urothelial carcinoma planned for treatment with any of the following at the genitourinary oncology clinics of Emory University's Winship Cancer Institute under the list FDA approved indications:
    - Pembrolizumab: first line for locally advanced or metastatic urothelial carcinoma who are not eligible for platinum-based chemotherapy; or second line for locally advanced or metastatic urothelial carcinoma after progression on platinum-based chemotherapy)
    - Avelumab: maintenance treatment in locally advanced or metastatic urothelial carcinoma following no progression on first-line platinum-containing chemotherapy
    - Nivolumab: adjuvant treatment of urothelial carcinoma in high risk of disease recurrence after undergoing radical resection
        - High risk disease as defined in Checkmate 274[9]: pathological stage of pT3, pT4a, or pN+ and patient not eligible for20 or declined adjuvant cisplatin-based combination chemotherapy for patients who had not received neoadjuvant cisplatin-based chemotherapy and pathological stage of ypT2 to ypT4a or ypN+ for patients who received neoadjuvant cisplatin
5. Patients must have adequate organ and marrow function, within 28 days of Cycle 1 Day 1, at the discretion of the investigator.
6. The effects of study drugs on the developing human fetus are unknown. For this reason, female of child-bearing potential (FCBP) must have a negative serum or urine pregnancy test prior to starting therapy.
7. FCBP and men treated or enrolled on this protocol must agree to use adequate contraception (hormonal or barrier method of birth control; abstinence) prior to study entry, for the duration of study participation, and 3 months after completion of study drug administration. Should a woman become pregnant or suspect she is pregnant while she or her partner is participating in this study, she should inform her treating physician immediately.
    - A female of childbearing potential (FCBP) is a sexually mature woman who: 1) has not undergone a hysterectomy or bilateral oophorectomy; or 2) has not been naturally postmenopausal for at least 24 consecutive months (i.e., has had menses at any time in the preceding 24 consecutive months).
8. Completion of all previous therapy (including surgery, radiotherapy, chemotherapy, immunotherapy, or investigational therapy) for the treatment of cancer **≥ 4 weeks** before the start of study therapy.
9. Patients with known history or current symptoms of cardiac disease, or history of treatment with cardiotoxic agents, should have a clinical risk assessment of cardiac function using the New York Heart Association Functional Classification (Appendix B). To be eligible for this trial, patients should be class IIB or better.
    - Patients without existing cardiac disease that raise the risk of complications who consent for the trial will proceed with trial participation.
    - Patients with existing cardiac disease that could raise the risk of complications will be referred at the discretion of the investigator to a cardio-oncologist who is a co-investigator on the trial (or general cardiologist) for cardiac optimization prior to starting propranolol.
10. Life expectancy > 12 weeks as determined by the Investigator.
11. Willingness and ability of the subject to comply with scheduled visits, drug administration plan, protocol-specified laboratory tests, other study procedures, and study restrictions.

12. Evidence of a personally signed informed consent indicating that the subject is aware of the neoplastic nature of the disease and has been informed of the procedures to be followed, the experimental nature of the therapy, alternatives, potential risks and discomforts, potential benefits, and other pertinent aspects of study participation.

Exclusion criteria

An individual who meets any of the following criteria will be excluded from participation in this study:

1. Patients who have had chemotherapy or radiotherapy within 4 weeks prior to entering the study or those who have not recovered from adverse events due to agents administered more than 4 weeks earlier (*i.e.*, have residual toxicities > Grade 2).
2. Patients who are receiving any other investigational agents or an investigational device within 21 days before administration of first dose of study drugs.
3. History of allergic reactions attributed to compounds of similar chemical or biologic composition to the agents used in study.
4. Contraindication to ICI per investigator discretion.
5. Uncontrolled current illness including, but not limited to, ongoing or active infection, symptomatic congestive heart failure, unstable angina pectoris, cardiac arrhythmia, or psychiatric illness/social situations that would limit compliance with study requirements.
6. Significant cardiovascular disease (e.g., myocardial infarction, arterial thromboembolism, cerebrovascular thromboembolism) within 3 months prior to start of study therapy; angina requiring therapy; symptomatic peripheral vascular disease; New York Heart Association Class 3 or 4 congestive heart failure; or uncontrolled Grade ≥3 hypertension (diastolic blood pressure ≥100 mmHg or systolic blood pressure ≥160 mmHg) despite antihypertensive therapy.
7. Contraindication to a beta blocker: cardiac conditions that significantly raise the risk of cardiopulmonary complications, including unstable angina, uncontrolled heart failure, symptomatic bradycardia, and severe asthma.
8. Current use of an oral or intravenous beta blocker (e.g. atenolol, bisoprolol, carvedilol, labetalol, metoprolol, nadolol, sotalol, among other beta blockers) with inability to safely switch to a non-beta blocker agent. The washout for current users should be at least 14 days with enough transition period.

10. Vulnerable Populations

N/A

11. Local Number of Participants

We will be recruiting 24 participants at Winship. Patients will be registered after signing of the informed consent document and meeting all entry requirements.

12. Recruitment Methods

Investigators, nurses (CRNs), research coordinators (CRCs) and/or data managers review lists of cancer patients who have cancer and will determine if there are patients who might be eligible for a clinical trial. The CRN/CRC/data manager reviews accessible medical records to screen further for eligibility. The CRN/CRC reviews the eligibility with the physician.

Subjects will be identified by their treating physicians. Clinical care team at Winship will inform potential subjects about the known benefits and potential risks of a clinical trial as well as other available treatment options. Some of the subjects recruited for this protocol will be patients being treated at Emory and under the care of one or more of the study investigators. Some potential subjects will be identified by their treating physician and referred to Emory for possible participation in the protocol.

No incentives are provided to patients for trial participation.

Study personnel will notify Winship Central Subject Registration (WCSR) by email at winshipcsr@emory.edu, once subject has been consented for a trial.

Email notification must be done within 24 hours after consent has been obtained and it will include scanned copies of:

- Signed patient consent form
- HIPAA authorization form
- Emory Research Management System (ERMS; *https://erms.emory.edu*) Enrollment Fax Cover

The WCSR will enter the subject into the OnCore Research Management System, which is the system of record for Winship Cancer Institute Clinical Trials.

Enrolling a subject requires careful screening and determination of eligibility.

Eligible patients will be enrolled on study centrally at Winship Cancer Institute by the Study Coordinator.

Assignment to ICI plus propranolol vs. ICI alone cohorts is not randomized and will be based on the physician-patient discussion. When all required test results are available, complete the eligibility checklist and provide the checklist and the supporting documentation to the IRB approved investigator for review and sign-off. OnCore and ERMS must be updated to reflect eligibility and on treatment status.

Following enrollment, patients should begin protocol treatment within 14 days. Issues that would cause treatment delays should be discussed with the Principal Investigator.

13. Withdrawal of Participants

Participants are free to withdraw from participation in the study at any time upon request.
An investigator may discontinue or withdraw a participant from the study for the following reasons:

- Pregnancy
- Significant study intervention non-compliance
- If any clinical adverse event (AE), laboratory abnormality, or other medical condition or situation occurs such that continued participation in the study would not be in the best interest of the participant
- Disease progression which requires discontinuation of the study intervention
- If the participant meets an exclusion criterion (either newly developed or not previously recognized) that precludes further study participation
- Participant unable to receive ICI +/- propranolol for over 30 days

The reason for participant discontinuation or withdrawal from the study will be recorded on the Case Report Form (CRF). Subjects who sign the informed consent form and are randomized but do not receive the study intervention may be replaced. Subjects who sign the informed consent form, and are randomized and receive

the study intervention, and subsequently withdraw, or are withdrawn or discontinued from the study, will be replaced.

14. Risks to Participants

Propranolol

Angina Pectoris
There have been reports of exacerbation of angina and, in some cases, myocardial infarction, following abrupt discontinuance of propranolol therapy. Therefore, when discontinuance of propranolol is planned, the dosage should be gradually reduced over at least a few weeks and the patient should be cautioned against interruption or cessation of therapy without the physician's advice. If propranolol therapy is interrupted and exacerbation of angina occurs, it usually is advisable to reinstitute propranolol therapy and take other measures appropriate for the management of angina pectoris. Since coronary artery disease may be unrecognized, it may be prudent to follow the above advice in patients considered at risk of having occult atherosclerotic heart disease who are given propranolol for other indications.

Hypersensitivity and Skin Reactions
Hypersensitivity reactions, including anaphylactic/anaphylactoid reactions, have been associated with the administration of propranolol (see ADVERSE REACTIONS). Cutaneous reactions, including Stevens - Johnson syndrome, toxic epidermal necrolysis, exfoliative dermatitis, erythema multiforme, and urticaria, have been reported with use of propranolol (see ADVERSE REACTIONS).

Cardiac Failure
Sympathetic stimulation may be a vital component supporting circulatory function in patients with congestive heart failure, and its inhibition by beta blockade may precipitate more severe failure. Although beta blockers should be avoided in overt congestive heart failure, some have been shown to be highly beneficial when used with close follow-up in patients with a history of failure who are well compensated and are receiving additional therapies, including diuretics as needed. Beta-adrenergic blocking agents do not abolish the inotropic action of digitalis on heart muscle.

In Patients without a History of Heart Failure, continued use of beta blockers can, in some cases, lead to cardiac failure.

Nonallergic Bronchospasm (e.g., Chronic Bronchitis, Emphysema)
In general, patients with bronchospastic lung disease should not receive beta blockers. Propranolol should be administered with caution in this setting since it may provoke a bronchial asthmatic attack by blocking bronchodilation produced by endogenous and exogenous catecholamine stimulation of beta-receptors.

Major Surgery
Chronically administered beta-blocking therapy should not be routinely withdrawn prior to major surgery, however the impaired ability of the heart to respond to reflex adrenergic stimuli may augment the risks of general anesthesia and surgical procedures.

Diabetes and Hypoglycemia
Beta-adrenergic blockade may prevent the appearance of certain premonitory signs and symptoms (pulse rate and pressure changes) of acute hypoglycemia, especially in labile insulin-dependent diabetics. In these patients, it may be more difficult to adjust the dosage of insulin. Propranolol therapy, particularly when given to infants

and children, diabetic or not, has been associated with hypoglycemia, especially during fasting as in preparation for surgery. Hypoglycemia has been reported in patients taking propranolol after prolonged physical exertion and in patients with renal insufficiency.

Thyrotoxicosis

Beta-adrenergic blockade may mask certain clinical signs of hyperthyroidism. Therefore, abrupt withdrawal of propranolol may be followed by an exacerbation of symptoms of hyperthyroidism, including thyroid storm. Propranolol may change thyroid-function tests, increasing T4 and reverse T3 and decreasing T3. Wolff-Parkinson-White Syndrome Beta-adrenergic blockade in patients with Wolf-Parkinson-White Syndrome and tachycardia has been associated with severe bradycardia requiring treatment with a pacemaker. In one case, this result was reported after an initial dose of 5 mg propranolol.

Pheochromocytoma

Blocking only the peripheral dilator (beta) action of epinephrine with propranolol leaves its constrictor (alpha) action unopposed. In the event of hemorrhage or shock, there is a disadvantage in having both beta and alpha blockade since the combination prevents the increase in heart rate and peripheral vasoconstriction needed to maintain blood pressure.

General Precautions

- Propranolol should be used with caution in patients with impaired hepatic or renal function. Propranolol is not indicated for the treatment of hypertensive emergencies.
- Beta-adrenergic receptor blockade can cause reduction of intraocular pressure. Patients should be told that Propranolol may interfere with the glaucoma screening test. Withdrawal may lead to a return of increased intraocular pressure.
- While taking beta blockers, patients with a history of severe anaphylactic reaction to a variety of allergens may be more reactive to repeated challenge, either accidental, diagnostic, or therapeutic. Such patients may be unresponsive to the usual doses of epinephrine used to treat allergic reaction.
- Mild symptoms of fatigue are common during the titration phase of propranolol. If those persist, the patient will be referred to the cardio-oncologist co-investigator.
- All patients will be provided with a dosing schedule, a home monitor for self-assessment of blood pressure and heart rate if they do not already have one, and a chart for daily recording of symptoms and hemodynamic data.
- Upon cessation of trial participation, propranolol will be weaned off over 3 days.

Clinical Laboratory Tests

In patients with hypertension, use of propranolol has been associated with elevated levels of serum potassium, serum transaminases and alkaline phosphatase. In severe heart failure, the use of propranolol has been associated with increases in Blood Urea Nitrogen.

Adverse Events

The following adverse events were observed and have been reported in patients using propranolol:
Cardiovascular: Bradycardia; congestive heart failure; intensification of AV block; hypotension; paresthesia of hands; thrombocytopenic purpura; arterial insufficiency, usually of the Raynaud type.
Central Nervous System: Light-headedness, mental depression manifested by insomnia, lassitude, weakness, fatigue; catatonia; visual disturbances; hallucinations; vivid dreams; an acute reversible syndrome characterized by disorientation for time and place, short-term memory loss, emotional lability, slightly clouded sensorium, and decreased performance on neuropsychometrics. For immediate-release formulations, fatigue, lethargy, and vivid dreams appear dose-related.

Gastrointestinal: Nausea, vomiting, epigastric distress, abdominal cramping, diarrhea, constipation, mesenteric arterial thrombosis, ischemic colitis.
Allergic: Hypersensitivity reactions, including anaphylactic/anaphylactoid reactions, pharyngitis and agranulocytosis; erythematous rash, fever combined with aching and sore throat; laryngospasm, and respiratory distress.
Respiratory: Bronchospasm.
Hematologic: Agranulocytosis, nonthrombocytopenic purpura, thrombocytopenic purpura.
Autoimmune: Systemic lupus erythematosus (SLE).
Skin and mucous membranes: Stevens-Johnson Syndrome, toxic epidermal necrolysis, dry eyes, exfoliative dermatitis, erythema multiforme, urticaria, alopecia, SLE-like reactions, and psoriasiform rashes. Oculomucocutaneous syndrome involving the skin, serous membranes and conjunctivae reported for a beta blocker (practolol) have not been associated with propranolol.
Genitourinary: Male impotence; Peyronie's disease

ICI (Pembrolizumab, Avelumab, Nivolumab)
ICI's most common adverse reactions (reported in ≥20% of patients) are fatigue, musculoskeletal pain, decreased appetite, pruritus, diarrhea, nausea, rash, pyrexia, cough, dyspnea, constipation, pain, and abdominal pain.

Other risks

- **Blood draws** - The physical risk of drawing blood is local pain and bruising at the site of venipuncture. Qualified phlebotomists or designee will draw blood samples. Care will be taken to obtain these specimens in a safe and hygienic manner. A small number of people experience lightheadedness or fainting. There is a slight risk of infection. To minimize these risks, attempts will be made to draw study blood samples at the same time as blood draws needed for routine clinical care are obtained. Repeated blood drawing may be associated with iron deficiency anemia.

- **Data security -** Subjects will be asked to provide personal health information (PHI). All attempts will be made to keep this PHI confidential within the limits of the law. However, there is a chance that unauthorized persons will see the subjects' PHI. All records will be kept in a locked file cabinet or maintained in a locked room at the participating sites. Electronic files will be password protected behind an academic institutional firewall. Only people who are involved in the conduct, oversight, monitoring, or auditing of this study will be allowed access to the PHI that is collected. Any publications from this study will not use information that will identify subjects. Organizations that may inspect and/or copy research records maintained at the participating sites for quality assurance and data analysis include groups such as the National Cancer Institute (NCI) and Food and Drug Administration (FDA).

15. Potential Benefits to Participants

There is no guarantee of benefit to subjects who enroll in this protocol.

16. Statistical consideration:

16. 1 Study Design and Sample Size

We plan to enroll up to 24 patients, 12 in the ICI plus propranolol cohort and 12 in the ICI alone cohort.

Descriptive statistics will be provided for collected data including demographics, safety/toxicity, overall response rate (for subjects receiving avelumab and pembrolizumab alone), overall survival, progression free survival, quality of life, molecular biomarkers, correlative changes in T-cells etc. as appropriate. Descriptive

statistics on continuous data will include means, medians, standard deviations, and ranges, while categorical data will be summarized using frequency counts and percentages. Safety analysis will follow an as-treated principle.

16.2 Population for Analysis Sets

Safety Analysis Set will include all subjects who received at least one dose of study drug(s).
Full Analysis Set (FAS) will include all subjects who received at least one dose of study drug.

16.3 Analysis of the safety and secondary endpoints.

Safety: Descriptive statistics will be used to summarize the toxicity profile of the intervention. Toxicities will be tabulated by grade, association, and cycle number.

Response: Descriptive statistics will be used to summarize overall response rate (for patients receiving avelumab and pembrolizumab), overall survival, and progression free survival.

Correlatives: Correlative changes in peripheral T-cell subsets, myeloid derived suppressor cells (MDSC), blood inflammatory markers and blood cytokines before and after treatment, will first be described by summary statistics. This would be separately for the ICI plus propranolol cohorts and the ICI alone cohort. Descriptive statistics on continuous data will include mean, median, standard deviation, and range (as well as geometric means and geometric coefficient of variation for PK parameters), while categorical data will be summarized using frequency counts and percentages. Graphical summaries of the data may be presented.

17. Data Management and Confidentiality

17.1 Data/specimens

Participant confidentiality is strictly held in trust by the participating investigators, their staff, and the sponsor(s) and their agents. Therefore, the study protocol, documentation, data, and all other information generated will be held in strict confidence. No information concerning the study or the data will be released to any unauthorized third party without prior written approval of the Principal Investigator. The study participant's contact information will be securely stored at each clinical site for internal use during the study. At the end of the study, all records will continue to be kept in a secure location for as long a period as dictated by local IRB and Institutional regulations.

Data and/or data forms will be submitted in the clinical management system - Online Collaborative Research Environment (ONCORE) - per Winship SOP 4.2 Data Completion Metrics.

All information in original records and certified copies of original records or clinical findings, observations, or other activities necessary for the reconstruction and evaluation of the trial is considered source data. Source data are contained in source documents, which can be original records or certified copies of hospital records, clinical and office charts, laboratory notes, memoranda, subjects' diaries of evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate and complete, 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.

Case Report Forms (CRFs) - Source data may be collected in the source documents or entered directly onto the case report forms.

All documentation of adverse events, records of study drug receipt and dispensation, and all IRB correspondence will be maintained for at least 2 years after the investigation is completed.

Study participant research data, which is for purposes of statistical analysis and scientific reporting, will be stored. This will not include the participant's contact or identifying information. Rather, individual participants and their research data will be identified by a unique study identification number. The study data entry and study management systems used by clinical sites and research staff will be secured and password protected. At the end of the study, all study databases will be de-identified and archived.

Samples and data collected under this protocol may be used to study urothelial carcinoma. Access to stored samples will be limited to IRB-approved investigators. Samples and data will be stored using codes assigned by the investigators or their designees. Data will be kept in password-protected computers. Only investigators will have access to the samples and data.

All stored samples will be maintained in the laboratory to which it was sent initially for analysis. Study participants who request destruction of samples will be notified of compliance with such request and all supporting details will be maintained for tracking.

18. Provisions to Monitor the Data to Ensure the Safety of Participants

Definition of Adverse Events (AE)

Adverse event means any untoward medical occurrence associated with the use of an intervention in humans, whether or not considered intervention-related (21 CFR 312.32 (a)).

Definition of Serious Adverse Events (SAE)

An adverse event (AE) or suspected adverse reaction is considered "serious" if, in the view of either the investigator or sponsor, it results in any of the following outcomes:

- Death
- Life-threatening adverse event
- Inpatient hospitalization or prolongation of existing hospitalization
- A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions, or a congenital anomaly/birth defect.
- Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the participant and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. (Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse).

Classification of an Adverse Event

Severity of Event

For adverse events (AEs) not included in the protocol defined grading system, the following guidelines will be used to describe severity.

- **Mild** – Events require minimal or no treatment and do not interfere with the participant's daily activities.
- **Moderate** – Events result in a low level of inconvenience or concern with the therapeutic measures. Moderate events may cause some interference with functioning.

- **Severe** – Events interrupt a participant's usual daily activity and may require systemic drug therapy or other treatment. Severe events are usually potentially life-threatening or incapacitating. Of note, the term "severe" does not necessarily equate to "serious".

Relationship to Study Intervention

All adverse events (AEs) must have their relationship to study intervention assessed by the clinician who examines and evaluates the participant based on temporal relationship and his/her clinical judgment. The degree of certainty about causality will be graded using the categories below. In a clinical trial, the study product must always be suspect.

- **Definitely Related** – There is clear evidence to suggest a causal relationship, and other possible contributing factors can be ruled out. The clinical event, including an abnormal laboratory test result, occurs in a plausible time relationship to study intervention administration and cannot be explained by concurrent disease or other drugs or chemicals. The response to withdrawal of the study intervention (dechallenge) should be clinically plausible. The event must be pharmacologically or phenomenologically definitive, with use of a satisfactory rechallenge procedure if necessary.
- **Probably Related** – There is evidence to suggest a causal relationship, and the influence of other factors is unlikely. The clinical event, including an abnormal laboratory test result, occurs within a reasonable time after administration of the study intervention, is unlikely to be attributed to concurrent disease or other drugs or chemicals, and follows a clinically reasonable response on withdrawal (dechallenge). Rechallenge information is not required to fulfill this definition.
- **Potentially Related** – There is some evidence to suggest a causal relationship (e.g., the event occurred within a reasonable time after administration of the trial medication). However, other factors may have contributed to the event (e.g., the participant's clinical condition, other concomitant events). Although an AE may rate only as "possibly related" soon after discovery, it can be flagged as requiring more information and later be upgraded to "probably related" or "definitely related", as appropriate.
- **Unlikely to be related** – A clinical event, including an abnormal laboratory test result, whose temporal relationship to study intervention administration makes a causal relationship improbable (e.g., the event did not occur within a reasonable time after administration of the study intervention) and in which other drugs or chemicals or underlying disease provides plausible explanations (e.g., the participant's clinical condition, other concomitant treatments).
- **Not Related** – The AE is completely independent of study intervention administration, and/or evidence exists that the event is definitely related to another etiology. There must be an alternative, definitive etiology documented by the clinician.

Adverse Event and Serious Adverse Event Reporting

Expectedness

Principal Investigator will be responsible for determining whether an adverse event (AE) is expected or unexpected. An AE will be considered unexpected if the nature, severity, or frequency of the event is not consistent with the risk information previously described for the study intervention.

Adverse Event Reporting

From the time of treatment allocation/randomization through 28 days following cessation of treatment, all adverse events, that begin or worsen after informed consent, must be recorded by the investigator or designee at each examination on the Adverse Event case report forms/worksheets.

The investigator will make every attempt to follow all subjects with non-serious adverse events for outcome.

Conditions that were already present at the time of informed consent should be recorded in the Medical History page of the patient's CRF/worksheet.

Adverse events will be assessed and graded according to the Common Terminology Criteria for Adverse Events (CTCAE) version 5.0. Grade 1 to 5 will be used to characterize the severity of the Adverse Event.
If CTCAE grading does not exist for an adverse event, the severity of mild, moderate, severe, and life-threatening, death related to the AE corresponding respectively to Grades 1 - 5, will be used. Information about any deaths (related to an Adverse Event or not) will also be collected through a Death form (or EOT/SEC/Survival Information in NOVDD). The occurrence of adverse events should be sought by non-directive questioning of the patient (patient) during the screening process after signing informed consent and at each visit during the study. Adverse events also may be detected when they are volunteered by the patient during the screening process or between visits, or through physical examination, laboratory test, or other assessments. As far as possible, each adverse event should be evaluated to determine:

1. The severity grade (CTCAE Grade 1-5)
2. Its duration (Start and end dates)
3. Its relationship to the study treatment (Reasonable possibility that AE is related: No, Yes) or its relationship to the study treatment (Reasonable possibility that AE is related: No, Yes, investigational treatment, Yes, the study treatment (non-investigational), Yes, both and/or indistinguishable)
4. Action taken with respect to study or investigational treatment (none, dose adjusted, temporarily interrupted, permanently discontinued, unknown, not applicable)
5. Whether medication or therapy was given (no concomitant medication/non-drug therapy, concomitant medication/non-drug therapy)
6. Whether it is serious, where a serious adverse event (SAE) is defined as in Section 9.2 and which seriousness criteria have been met (include for NCDS trials).
7. Outcome (not recovered/not resolved, recovered/resolved, recovering/resolving, recovered/resolved with sequelae, fatal, unknown)

If the event worsens the event should be reported a second time in the CRF noting the start date when the event worsens in toxicity. For grade 3 and 4 adverse events only, if improvement to a lower grade is determined a new entry for this event should be reported in the CRF noting the start date when the event improved from having been Grade 3 or Grade 4. All adverse events should be treated appropriately. If a concomitant medication or non-drug therapy is given, this action should be recorded on the Adverse Event CRF.

Once an adverse event is detected, it should be followed until its resolution or until it is judged to be permanent, and assessment should be made at each visit (or more frequently, if necessary) of any changes in severity, the suspected relationship to the study treatment, the interventions required to treat it, and the outcome. Progression of malignancy (including fatal outcomes), if documented by use of appropriate method (for example, as per RECIST criteria for solid tumors), should not be reported as a serious adverse event.

Adverse events separate from the progression of malignancy (example, deep vein thrombosis at the time of progression or hemoptysis concurrent with finding of disease progression) will be reported as per usual guidelines used for such events with proper attribution regarding relatedness to the drug.

Laboratory abnormalities that constitute an Adverse event in their own right (are considered clinically significant, induce clinical signs or symptoms, require concomitant therapy or require changes in study treatment), should be recorded on the Adverse Events CRF.

Laboratory abnormalities, that do not meet the definition of an adverse event, should not be reported as adverse events. A Grade 3 or 4 event (severe) as per CTCAE does not automatically indicate a SAE unless it meets

the definition of serious as defined below and/or as per investigator's discretion. A dose hold or medication for the lab abnormality may be required by the protocol in which case the lab abnormality would still, by definition, be an adverse event and must be reported as such.

Serious Adverse Event Reporting

For the time period beginning at treatment allocation/randomization through 28 days following cessation of treatment, or 28 days following cessation of treatment if the subject initiates new anticancer therapy, whichever is earlier, any serious adverse event, or follow up to a serious adverse event, including death due to any cause whether or not related to the study drug, must be **submitted on an SAE form** and assessed by PI in order to determine reporting criteria to IRB, DSMC, FDA, supporter or IND Sponsor.

All SAEs will be followed until satisfactory resolution or until the site investigator deems the event to be chronic or the adherence to be stable. Other supporting documentation of the event may be requested by the IND sponsor and should be provided as soon as possible. The IND sponsor will be responsible for notifying FDA of any unexpected fatal or life-threatening suspected adverse reaction as soon as possible but in no case later than 7 calendar days after the sponsor's initial receipt of the information.

Reporting to study supporter/IRB and or FDA

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

Any additional information for the SAE including complications, progression of the initial SAE, and recurrent episodes must be reported to the principal investigator as follow-up to the original episode **within 2 days** of the investigator receiving the follow-up information.

An SAE occurring at a different time interval or otherwise considered completely unrelated to a previously reported one should be reported separately as a new event.

Any SAEs experienced after the reporting period described above should only be reported to FDA/IRB if the investigator suspects a causal relationship to the study treatment.

Information about all SAEs is collected and recorded on the **Serious Adverse Event Report Form**; all applicable sections of the form must be completed in order to provide a clinically thorough report. The investigator must assess and record the relationship of each SAE to each specific study treatment (if there is more than one study treatment), complete the SAE Report Form, and submit the completed form.

Each reoccurrence, complication, or progression of the original event should be reported as a follow-up to that event regardless of when it occurs. The follow-up information should describe whether the event has resolved or continues, if and how it was treated, whether the blind was broken or not, and whether the patient continued or withdrew from study participation.

Definition of unanticipated problems (UP) and reporting requirements

The Office for Human Research Protections (OHRP) considers unanticipated problems involving risks to participants or others to include, in general, any incident, experience, or an outcome that meets **all** the following criteria: Unexpected in terms of nature, severity, or frequency given (a) the research procedures that are described in the protocol-related documents, such as the IRB-approved research protocol and informed consent

document; and (b) the characteristics of the participant population being studied; Related or possibly related to participation in the research ("possibly related" means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research); and Suggests that the research places participants or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized. This study will use the OHRP definition of unanticipated problems. Incidents or events that meet the OHRP criteria for UPs require the creation and completion of a UP report form. It is the site investigator's responsibility to report UPs to their IRB and to the DCC/study sponsor. The UP report will include the following information: Protocol identifying information: protocol title and number, PI's name, and the IRB project number; A detailed description of the event, incident, experience, or outcome; An explanation of the basis for determining that the event, incident, experience, or outcome represents an UP; A description of any changes to the protocol or other corrective actions that have been taken or are proposed in response to the UP. The IND sponsor will make an assessment of whether the event constitutes an unanticipated problem posing risks to subjects or others (UP). This assessment will be provided to the Emory University IRB. If the Emory IRB determines an event is a UP it will notify the appropriate regulatory agencies and institutional officials.

The Data and Safety Monitoring Committee (DSMC)

The Data and Safety Monitoring Committee (DSMC) of the Winship Cancer Institute will provide oversight for the conduct of this study. The DSMC functions independently within Winship Cancer Institute to conduct internal monitoring functions to ensure that research being conducted by Winship Cancer Institute Investigators produces high-quality scientific data in a manner consistent with good clinical practice (GCP) and appropriate regulations that govern clinical research. Since this is a Simon 2-Stage design study, The PI or designee must provide the DSMC a report outlining the overall enrollment and path to decision to open the next enrollment cohort. Depending on the risk level of the protocol as determined by CTRC, the DSMC review may occur every 6 months or annually. For studies deemed Moderate Risk, initial study monitoring will occur within 1 year from the date of the first subject accrued, with 2 of the first 5 subjects being reviewed. Subsequent monitoring will occur in routine intervals per the Winship Data and Safety Monitoring Plan (DSMP). The DSMC will review pertinent aspects of the study to assess subject safety, compliance with the protocol, data collection, and risk-benefit ratio. Specifically, the Winship Cancer Institute Internal Monitors assigned to the DSMC may verify informed consent, eligibility, data entry, accuracy and availability of source documents, AEs/SAEs, and essential regulatory documents. Following the monitoring review, monitors will provide a preliminary report of monitoring findings to the PI and other pertinent individuals involved in the conduct of the study. The PI is required to address and respond to all the deficiencies noted in the preliminary report. Prior to the completion of the final summary report, monitors will discuss the preliminary report responses with the PI and other team members (when appropriate). A final monitoring summary report will then be prepared by the monitor. Final DSMC review will include the final monitoring summary report with corresponding PI response, submitted CAPA (when applicable), PI Summary statement, and available aggregate toxicity and safety data. The DSMC will render a recommendation and rating based on the overall trial conduct. The PI is responsible for ensuring that instances of egregious data insufficiencies are reported to the IRB. Continuing Review submissions will include the DSMC recommendation letter. Should any revisions be made to the protocol-specific monitoring plan after initial DSMC approval, the PI will be responsible for notifying the DSMC of such changes. The Committee reserves the right to conduct additional audits if necessary.

19. Provisions to Protect the Privacy Interests of Participants

Participants will be assured of their voluntary participation in the study, their choice to answer or not answer any question, and the protocol for maintaining confidentiality.

Participant confidentiality is strictly held in trust by the participating investigators, their staff, and the sponsor(s) and their agents. This confidentiality is extended to cover testing of biological samples and genetic tests in addition to the clinical information relating to participants. Therefore, the study protocol, documentation, data, and all other information generated will be held in strict confidence. No information concerning the study or the data will be released to any unauthorized third party without prior written approval of the sponsor.

The study monitor, other authorized representatives of the sponsor, representatives of the IRB or pharmaceutical company supplying study product may inspect all documents and records required to be maintained by the investigator, including but not limited to, medical records (office, clinic, or hospital) and pharmacy records for the participants in this study. The clinical study site will permit access to such records.

The study participant's contact information will be securely stored at each clinical site for internal use during the study. At the end of the study, all records will continue to be kept in a secure location for as long a period as dictated by local IRB and Institutional regulations.

Study participant research data, which is for purposes of statistical analysis and scientific reporting, will be transmitted to and stored. This will not include the participant's contact or identifying information. Rather, individual participants and their research data will be identified by a unique study identification number. The study data entry and study management systems used by clinical sites and research staff will be secured and password protected. At the end of the study, all study databases will be de-identified and archived

20. Economic Burden to Participants

The study sponsor will pay for certain items and services the subject may receive in this study. Specifically, the cost of propranolol will be covered by the sponsor (being the study drug) for patients on the ICI plus propranolol cohort while ICI will be covered as part of the patient's regular medical care (being an FDA-approved standard of care for the trial's patient population). Subjects will have to pay for the items or services for which the study sponsor does not pay. The sponsor will not pay for regular medical care. If subjects have insurance, Emory will submit claims to the insurance for items and services that the sponsor does not cover. Emory will send in only those claims for items and services that it reasonably believes the insurance will pay and that the sponsor has not paid. The actual amount that participants have to pay depends on whether or not they have health insurance and whether or not that insurance will pay for any research study costs. Generally, insurance companies will not pay for items and services that are required just for a research study. Some insurance companies will not pay for regular medical treatment or treatment for complications if in a study. If subject do not have insurance, Emory will review that particular case as part of its program for low-income patient care. The standard policies of that program will apply. The program will figure out if subjects have to pay any costs for taking part in the study and what those costs will be.

21. Consent Process

The initial informed consent discussion will occur in Winship Cancer Institute or the Emory Clinic. At Winship Cancer Institute, the informed consent is an ongoing, interactive process rather than a one-time information session. The consent form document is designed to begin the informed consent process, which provides the patient with ongoing explanations that will help them make educational decisions about whether to begin or continue participating in the trial. The research team knows that a written document alone may not ensure that the patient fully understands what participation means. Therefore, the research team will discuss with the patient the trial's purpose, procedures, risks and potential benefits, and their rights as a participant. The team will continue to update the patient on any new information that may affect their situation.

Consent will be obtained prior to any research-driven procedures. The investigator will assess the patient's capacity during his/her encounters with him or her. The investigator will give the person providing consent adequate opportunity to read the consent document before it is signed and dated.

It will be explained to prospective participants that the study involves research, the purpose of the research, the expected duration of participation, as well as the approximate number of participants to be enrolled. The study procedures, and identification of research procedures v. non-research will also be thoroughly discussed. It will be explained to participants that participation is voluntary and that the subject may discontinue at any time.

Refusal to participate or withdraw will not involve a penalty or loss of benefits to which the participant is otherwise entitled. Refusal will in no way affect the participant's future are. The participant will also be told of the possible consequences of the decision to withdraw from the research, and procedures for orderly termination of participation.

Any significant new findings developed during the course of the research that may affect the participant's willingness to continue to participate will be provided. Also explained will be anticipated circumstances under which the subject's participation may be terminated by the investigator without the participant's consent.
Prospective participants will be provided with a description of any reasonably foreseeable risks or discomforts as well as a description of any benefits to the participant or to others that might be reasons expected from the research. Alternative procedures or courses of treatment will also be thoroughly discussed.

Prospective participants will also be given detailed information describing the extent to which confidentiality of records identifying the participant will be maintained and what records may be examined by the research staff, IRBs, sponsor, their representatives, and possibly the FDA or OHRP.

Also communicated to the participant will be an explanation that emergency medical care will be arranged for a study-related illness or injury, and an explanation of whether funds are set aside to pay for this care and/or compensation, and if so by whom (e.g., sponsor, subject, insurer). The participant is told the source of the study's funding.

All participants will be told of any additional costs that may result from participation in the research.

Non-English-Speaking Participants

A certified translator/interpreter will be present during the consenting process and all questions and concerns will be answered by the treating physician.

A Short Form in that specific language will be used. A certified translator/interpreter will be present during the consenting process and this will be documented. We will use what's available on Emory IRB website. For the languages that are not available, we will have the short form translated to that language and submit the IRB for review and approval prior to use. Process to Document Consent in Writing: Winship SOP 2.1:" Obtaining Informed consent for Interventional clinical trial" will be followed.

Participants who are not yet adults (infants, children, teenagers) : N/A

Cognitively Impaired Adults: N/A

Adults Unable to Consent: N/A

Waiver or Alteration of Consent Process (consent will not be obtained, required information will not be disclosed, or the research involves deception) N/A

22. Setting

The research will be conducted at Emory University.

Potential participants will be identified in medical oncology clinics, multidisciplinary cancer clinic, surgical oncology clinics, and multidisciplinary tumor board at Winship Cancer Institute of Emory University clinical practice sites (Emory University Hospital campus, Emory University Hospital Midtown campus, Emory Saint Joseph's Hospital, Grady Memorial Hospital).

23. Resources Available

Emory University was founded in 1836 and is a national center for teaching, research, and service. Emory University has been named as one of the nation's top 25 universities for more than a decade by the U.S. News and World Report. Emory University research partners include the Georgia Institute of Technology, the University of Georgia, Morehouse School of Medicine, the US Centers for Disease Control and Prevention, Children's Healthcare of Atlanta, and the Georgia Clinical and Translational Science Alliance (GACTSA). Emory University researchers received $734 million from external funding agencies in fiscal year 2018, including approximately $441 million in funding from federal agencies, $359 million of this from the National Institutes of Health (NIH).

Winship Cancer Institute (Winship) is Georgia's first and only National Cancer Institute (NCI)-designated Comprehensive Cancer Center (P30CA138292) and is dedicated to the integration of innovative clinical and basic science research with outstanding patient care for the prevention, treatment and control of cancer. First designated in 2009, Winship's NCI designation was renewed in 2012 and 2016, achieving an "outstanding" rating. Winship earned the prestigious Comprehensive Cancer Center designation from the NCI in 2016, after demonstrating that its outstanding programs are reducing the cancer burden on the state of Georgia through research conducted in its laboratories, its clinical trial program, and its population-based science. The institutional support for Winship was rated as 'exceptional' by the review panel.

The **Winship Clinic Building C** houses the primary offices and clinical space for cancer services including the medical oncology, hematology, and surgical oncology clinics, the radiation oncology program, and the Winship Ambulatory Infusion Center. In summer 2017, Emory Healthcare completed the expansion of **Emory University Hospital Tower** on Clifton Road. This nine-floor facility adds 144 inpatient beds to the hospital, of which more than 80% are dedicated to cancer care. The hospital expansion also accommodates cancer patient-specific intensive care units, an expanded BMT Unit with peri-transplant clinics to facilitate continuity of care, and a 24-hour cancer urgent care center, which serves as both a triage facility and short stay treatment center for patients with cancer-related medical concerns.

The **Winship Phase I Unit**, on the fourth floor of the Emory University Hospital Tower, is the largest unit in Georgia dedicated to the earliest and most critical phase of new cancer therapy evaluation. There is space for 15 private treatment bays, four clinic rooms, its own lab for doing patient blood work, a dedicated secure medication room, computer workspace for research and other support staff, and a "fast track" bay with three chairs for rapid use in patients who, for example, might need only a research lab test done.

The **Winship at Emory University Hospital Midtown** offers clinical space for specialized cancer care including gynecological oncology, surgical oncology, head & neck program, benign hematology, medical oncology, and the Ambulatory Infusion Center.

The **Winship at Emory Saint Joseph** offers clinical space for a variety of specialized cancer care by Emory-employed physicians, advanced practice providers, nurses, and clinical care team.

The **Georgia Cancer Center for Excellence at Grady Health System** services a critical role to Atlanta's population by being committed to providing the best possible care to all members of the community, regardless of their financial means. The Center is primarily staffed by Emory-employed physicians along with Emory-employed clinical trial research coordinators.

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APPENDIX A Performance Status Criteria

ECOG Performance Status Scale		**Karnofsky Performance Scale**	
Grade	Descriptions	Percent	Description
0	Normal activity. Fully active, able to carry on all pre-disease performance without restriction.	100	Normal, no complaints, no evidence of disease.
		90	Able to carry on normal activity; minor signs or symptoms of disease.
1	Symptoms, but ambulatory. Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature (*e.g.*, light housework, office work).	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.
2	In bed <50% of the time. Ambulatory and capable of all self-care, but unable to carry out any work activities. Up and about more than 50% of waking hours.	60	Requires occasional assistance but is able to care for most of his/her needs.
		50	Requires considerable assistance and frequent medical care.
3	In bed >50% of the time. Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.	40	Disabled, requires special care and assistance.
		30	Severely disabled, hospitalization indicated. Death not imminent.
4	100% bedridden. Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.	20	Very sick, hospitalization indicated. Death not imminent.
		10	Moribund, fatal processes progressing rapidly.
5	Dead.	0	Dead.

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

APPENDIX B New York Heart Association (NYHA) Functional Classification

The NYHA Functional Classification consists of a Patient Symptoms (I to IV) score and an Objective Assessment (A to D) score.

Class	Patient Symptoms
I	No limitation of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, dyspnea (shortness of breath).
II	Slight limitation of physical activity. Comfortable at rest. Ordinary physical activity results in fatigue, palpitation, dyspnea (shortness of breath).
III	Marked limitation of physical activity. Comfortable at rest. Less than ordinary activity causes fatigue, palpitation, or dyspnea.
IV	Unable to carry on any physical activity without discomfort. Symptoms of heart failure at rest. If any physical activity is undertaken, discomfort increases.

Class	Objective Assessment
A	No objective evidence of cardiovascular disease. No symptoms and no limitation in ordinary physical activity.
B	Objective evidence of minimal cardiovascular disease. Mild symptoms and slight limitation during ordinary activity. Comfortable at rest.
C	Objective evidence of moderately severe cardiovascular disease. Marked limitation in activity due to symptoms, even during less-than-ordinary activity. Comfortable only at rest.
D	Objective evidence of severe cardiovascular disease. Severe limitations. Experiences symptoms even while at rest.

As published in American Heart Association website – Classes of Heart Failure – accessed 07/20/20:
https://www.heart.org/en/health-topics/heart-failure/what-is-heart-failure/classes-of-heart-failure

APPENDIX C Drug Diary

Study ID: WINSHIP5200-20	
Subject Initials: _____ Subject ID: _____ Arm: _____ Cycle: _____	
Instructions:	Planned Dose: _____ mg BID po
Reminders:	1.
	2.

Day	Date	Time	# of tablets taken	Comments
1				
2				
3				
4				
5				
6				
7				
8				
9				
10				
11				
12				
13				
14				
15				
16				
17				
18				
19				
20				
21				
22				
23				
24				
25				
26				
27				
28				
29				
30				
31				
32				

Day	Date	Time	# of tablets taken	Comments
33				
34				
35				
36				
37				
38				
39				
40				
41				
42				

Record all medications taken during this cycle for example prescriptions and over-the-counter medications including vitamins.

Name of Medication	Reason for taking medication	Dose	How many times per day?	Date Medication Started	Date Medication Stopped

If you have any questions, please call: _____

APPENDIX D Patient-reported Outcome Questionnaire - NFBlSI-18 tool

Study ID: WINSHIP5200-20			
Subject Initials: _____	Subject ID: _____	Arm: _____	Cycle: _____

This questionnaire asks about your health and feelings. For each question, please rate your response from 0 (not at all) to 4 (very much) by writing an X in the one box that best describes your answer.

		0 = 'not at all'	**1**	**2**	**3**	**4 = 'very much'**
Subscale	**Item**					
Disease-related symptoms						
	I have pain					
	I am losing weight					
	I have trouble controlling my urine					
	I feel weak all over					
	I feel light-headed (dizzy)					
	Because of my physical condition, I have trouble meeting the needs of my family					
	I worry that my condition will get worse					
	I feel sad					
	I have a good appetite					
	(For men only) I am able to have and maintain an erection					
Treatment side effects						
	I am sleeping well					
	I have nausea					
	I have a lack of energy					
	I feel ill					
	I have control of my bowels					
	I am bothered by side effects of treatment					
General function/ well-being						
	I am able to enjoy life					
	I am content with the quality of my life right now					

APPENDIX E Abbreviations and definition of terms

The following abbreviations and special terms are used in this study Clinical Study Protocol.

Abbreviation or special term	Explanation
AE	Adverse event
ALK	Anaplastic lymphoma kinase
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
BoR	Best objective response
BP	Blood pressure
C	Cycle
CL	Clearance
C_{max}	Maximum plasma concentration
$C_{max,ss}$	Maximum plasma concentration at steady state
CR	Complete response
CT	Computed tomography
CTCAE	Common Terminology Criteria for Adverse Event
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic case report form
EDoR	Expected duration of response
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GI	Gastrointestinal
GMP	Good Manufacturing Practice
hCG	Human chorionic gonadotropin
IB	Investigator's Brochure
ICF	Informed consent form
IFN	Interferon
IgE	Immunoglobulin E
IgG	Immunoglobulin G
IHC	Immunohistochemistry

Abbreviation or special term	Explanation
IL	Interleukin
IP	Investigational product
irAE	Immune-related adverse event
IRB	Institutional Review Board
IV	Intravenous
MRI	Magnetic resonance imaging
NCI	National Cancer Institute
ORR	Objective response rate
OS	Overall survival
PBMC	Peripheral blood mononuclear cell
PD	Progressive disease
PFS	Progression-free survival
PFS2	Time to second progression
PGx	Pharmacogenetic research
PK	Pharmacokinetic(s)
PR	Partial response
q2w	Every 2 weeks
QTcF	QT interval corrected for heart rate using Fridericia's formula
RECIST 1.1	Response Evaluation Criteria in Solid Tumors, version 1.1
RR	Response rate
SAE	Serious adverse event
SD	Stable disease
SoC	Standard of Care
ULN	Upper limit of normal