Update #03

ALLIANCE FOR CLINICAL TRIALS IN ONCOLOGY

PROTOCOL UPDATE FOR A031901

DURATION OF IMMUNE CHECKPOINT THERAPY IN LOCALLY ADVANCED OR METASTATIC UROTHELIAL CARCINOMA: A RANDOMIZED PHASE 3 NON-INFERIORITY TRIAL (IMAGINE)

Study Exempt from IND Requirements per 21 CFR 312.2(b)

Commercial agents: Pembrolizumab (NSC #776864), Nivolumab (NSC #748726), Atezolizumab (NSC #783608), Avelumab (NSC #799232)

[X]	**Update:**	[ ]	**Status Change:**
[ ]	Eligibility changes	[ ]	Activation
[X]	Therapy / Dose Modifications / Study Calendar changes	[ ]	Closure
[X]	Informed Consent changes	[ ]	Suspension / temporary closure
[ ]	Scientific / Statistical Considerations changes	[ ]	Reactivation
[ ]	Data Submission / Forms changes		
[ ]	Editorial / Administrative changes		
[ ]	Other		

The changes included in this update to A031901 have been made in response to the NCI Action Letter from [redacted] This Action Letter is posted on the A031901 study page on the CTSU website. A revised CAEPR for pembrolizumab with new risks has been added to the protocol. The model consent form has been updated, however, there are no changes to the risk/benefit ratio.

Reconsent is not required, please follow the policy of your IRB of record regarding notifying patients of new information contained in this update.

No recommended level of IRB review is provided by the Alliance since the CIRB is the IRB of record for this trial. This amendment must be implemented within 30 days after posting. Please refer to the CIRB amendment application and CIRB guidelines for further instructions.

UPDATES TO THE PROTOCOL:

Section 8.2.1 Dose Management Guidelines for Pembrolizumab

- "Dose Modifications" and "Dose Modification and Toxicity Management for Immune-related Adverse Events Associated with Pembrolizumab" information has been added per NCI's updated dose modification guidelines for pembrolizumab.
- The table "Dose Modification and Toxicity Management Guidelines for Immune-related AEs and Infusion Reactions Associated with Pembrolizumab" has been updated.
- The new table, "Infusion-Related Reactions" has been added.
-The new table, "Neurology Toxicites" has been added.

UPDATES TO THE REGISTRATION MODEL CONSENT:

Possible Side Effects of Pembrolizumab

The word pembroluzimab was amended to Pembroluzimab (MK-3475).

- Decrease in Risk Attribution:
  - Changed to Also Reported on Pembrolizumab (MK-3475) Trials But With Insufficient Evidence for Attribution from Occasional (i.e., removed from the Risk Profile): Fluid in the joints; Pain in chest
- Deleted Risk:
  - Occasional: Infection
- Provided Further Clarification:
  - Rare: Changed from "Swelling and redness of the eye" to "Swelling and redness of the eye which may cause blurred vision with a chance of blindness"

A replacement protocol and model consent have been issued.

ATTACH TO THE FRONT OF EVERY COPY OF THIS PROTOCOL

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ClinicalTrials.gov Identifier: NCT 04637594

Study Chair

[redacted]

Study Co-Chair

[redacted]

QOL Co-chair

[redacted]

Health Economics Co-chair

[redacted]

Correlative Committee Chair

[redacted]

NRG Oncology Champion

[redacted]

ECOG-ACRIN Champion

[redacted]

SWOG Champion

[redacted]

Community Onc Co-chair

[redacted]

Disease Committee Chair

[redacted]

Modality Committee Chair

[redacted]

Primary Statistician

[redacted]

QOL Statistician

[redacted]

Secondary Statistician

[redacted]

Protocol Coordinator

[redacted]

Data Manager

[redacted]

Participating Organizations
Alliance/Alliance for Clinical Trials in Oncology (lead), ECOG-ACRIN/ECOG-ACRIN Cancer Research Group, NRG/NRG Oncology, SWOG/SWOG

Study Resources:

Expedited Adverse Event Reporting

[redacted]

Medidata Rave® iMedidata portal

[redacted]

OPEN (Oncology Patient Enrollment Network)

[redacted]

Biospecimen Management System

[redacted]

Protocol Contacts:

A031901 Nursing Contact

[redacted]

A031901 Pharmacy Contact

[redacted]

IROC

[redacted]

Protocol-related questions may be directed as follows:	
Questions	**Contact (via email)**
Questions regarding patient eligibility, treatment, and dose modification:	Study Chair, Nursing Contact, Protocol Coordinator, and (where applicable) Data Manager
Questions related to data submission, RAVE or patient follow-up:	Data Manager
Questions regarding the protocol document and model informed consent:	Protocol Coordinator
Questions related to IRB review	Alliance Regulatory Inbox [redacted]
Questions regarding CTEP-AERS reporting:	Alliance Pharmacovigilance Inbox [redacted]
Questions regarding specimens/specimen submissions:	Alliance Biorepository
Questions regarding drug administration	Pharmacy Contact

CANCER TRIALS SUPPORT UNIT (CTSU) ADDRESS AND CONTACT INFORMATION

CONTACT INFORMATION		
For regulatory requirements:	**For patient enrollments:**	**For data submission:**
Regulatory documentation must be submitted to the CTSU via the Regulatory Submission Portal. (Sign in at [redacted], and select the Regulatory > Regulatory Submission.) Institutions with patients waiting that are unable to use the Portal should alert the CTSU Regulatory Office immediately at [redacted] to receive further instruction and support. Contact the CTSU Regulatory Help Desk at [redacted] for regulatory assistance.	Refer to the patient enrollment section of the protocol for instructions on using the Oncology Patient Enrollment Network (OPEN). OPEN is accessed at [redacted] Contact the CTSU Help Desk with any OPEN related questions by phone or email : [redacted]	Data collection for this study will be done exclusively through Medidata Rave. Refer to the data submission section of the protocol for further instructions. Do not submit study data or forms to the CTSU. Do not copy the CTSU on data submissions.
The most current version of the **study protocol and all supporting documents** must be downloaded from the protocol-specific page located on the CTSU members' website [redacted] Access to the CTSU members' website is managed through the Cancer Therapy and Evaluation Program - Identity and Access Management (CTEP-IAM) registration system and requires log in with a CTEP-IAM username and password. : Permission to view and download this protocol and its supporting documents is restricted and is based on person and site roster assignment housed in the CTSU Regulatory Support System (RSS).		
Institutions will order the following supplies from the CTSU Operations Office: the QOL booklets. Supplies can be ordered by downloading and completing the CTSU Supply Request Form (available on the protocol-specific page on the CTSU website) and submitting it as instructed on the form.		
For clinical questions (i.e. patient eligibility or treatment-related) see the Protocol Contacts, Page 2.		
For non-clinical questions (i.e. unrelated to patient eligibility, treatment, or clinical data submission) Contact the CTSU Help Desk by phone or email: CTSU General Information Line – [redacted] All calls and correspondence will be triaged to the appropriate CTSU representative.		

DURATION OF IMMUNE CHECKPOINT THERAPY IN LOCALLY ADVANCED OR METASTATIC UROTHELIAL CARCINOMA: A RANDOMIZED PHASE 3 NON-INFERIORITY TRIAL (IMAGINE)

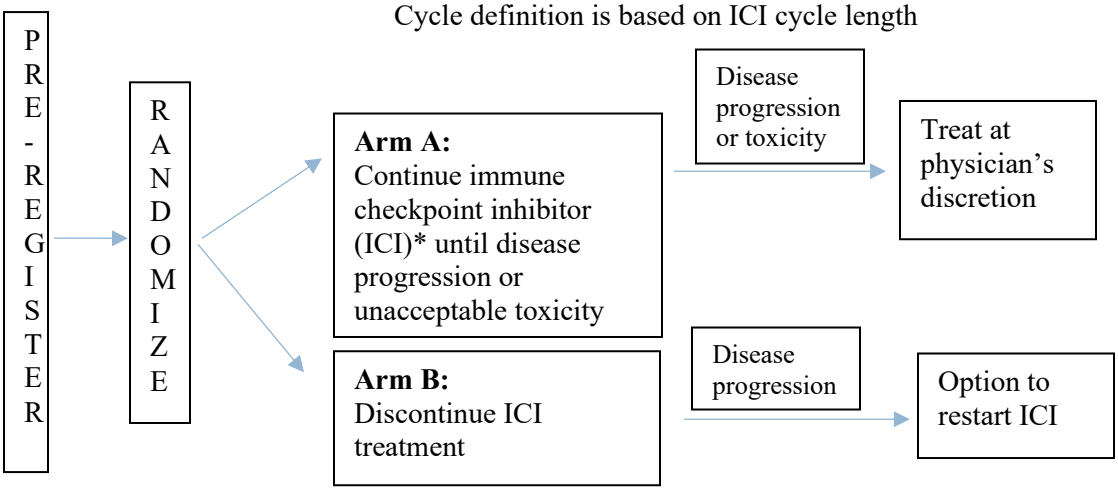
Commercial agents: Pembrolizumab, Nivolumab, Atezolizumab, Avelumab

Pre- registration Eligibility Criteria
Histologic or cytologic confirmed urothelial carcinoma
Locally advanced or metastatic
At least 1 cycle of active treatment with standard of care ICI
At least one scan showing CR, PR or SD (no PD)
No history of allogeneic organ transplant

Pre-reg and Reg Required Lab Values
Patients must have adequate bone marrow and organ function to continue PD-L1 ICI as judged by the treating physician. No specific parameters need to be met.

Registration Eligibility Criteria
No PD per RECIST v1.1 after 12-18 months of ICI
No ICI toxicity that makes treatment continuation unacceptable
Age ≥ 18 years
ECOG PS 0-2
CNS disease allowed if stable
No immunosuppressive medication exceeding 10 mg/day of prednisone or equivalent
Non-pregnant and non-nursing

Schema
Cycle definition is based on ICI cycle length



* ICI agents include pembrolizumab, nivolumab, atezolizumab, and avelumab

Patients will be followed for 5 years or until death or withdrawal of consent, whichever occurs first.
Please refer to the full protocol text for a complete description of the eligibility criteria and treatment plan.

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1.0 BACKGROUND

Immune checkpoint inhibitors that target negative regulators of the immune system, particularly the PD1/PD-L1 axis, have changed the paradigm of treatment for multiple advanced malignancies, including locally advanced or metastatic urothelial carcinoma (UC). The current standard of care is to administer PD-1 and PD-L1 blocking antibodies until disease progression or intolerable toxicity, with consideration of stopping treatment at 24 months in patients without disease progression. The optimal duration of therapy remains undefined. This is a prospective multicenter, randomized, open-label, phase 3 non-inferiority trial comparing PD-1/L1 ICI continuation (Arm A) versus discontinuation (Arm B) in patients with locally advanced or metastatic UC. Eligible patients must have investigator-assessed radiographic response, defined as any % decrease in target lesion(s) by RECIST 1.1 criteria (confirmed), without evidence of disease progression 12-18 months after initiating a standard of care PD1-/L1 containing regimen. The primary endpoint is overall survival.

1.1 Mechanism of action of immunotherapy and potential for durable benefit after treatment discontinuation

Immunotherapies have a different mechanism of action compared to traditional cytotoxic or targeted biological agents. The goal of immunotherapy is to harness long-term memory of the adaptive anti-tumor immune response to achieve durable tumor regression and potential cure. In preclinical models, successful immunotherapy given in a finite number of treatments leads to tumor rejection, and mice are protected from tumor re-challenge, consistent with the development of immunologic memory **(1-4)**. Lymphocyte depletion experiments have demonstrated that protection from tumor re-challenge are T-cell dependent **(3,4)**. In the clinic, immunotherapy strategies including high-dose interleukin 2 (IL-2) in advanced renal cell carcinoma (RCC) and chimeric antigen receptor (CAR)-modified T cells targeting CD19 in advanced B-cell hematologic malignancies, are administered in a finite number of doses and lead to durable survival benefit in the subgroup of patients who achieve deep objective responses **(5,6)**. Emerging data indicates that patients who stop anti-PD-1 or anti-PD-L1 inhibitors early may still derive benefit beyond treatment discontinuation (See below).

1.2 Immune checkpoint blockade in advanced UC

Urothelial carcinoma (UC) is the most common malignancy in the urinary tract, and accounts for approximately 16,000 deaths annually in the U.S. **(7)**. Approximately 10%-15% of patients initially diagnosed with non-muscle invasive bladder cancer (NMIBC) later develop invasive, locally advanced, and metastatic disease, and approximately 10% of patients present with locally advanced or metastatic disease at initial diagnosis. The standard of care for patients with locally advanced or metastatic UC is cisplatin-containing chemotherapy; however, many patients are cisplatin-ineligible due to comorbidities, including renal dysfunction, hearing impairment, and peripheral neuropathy. Since May 2016, monoclonal antibodies that disrupt the interaction of PD-1 and PD-L1 are rapidly approved for the management of locally advanced and metastatic UC.

PD-1 and PD-L1 inhibitors approved for locally advanced or metastatic UC include pembrolizumab, atezolizumab, nivolumab, and avelumab in patients whose disease progressed during or after platinum-containing chemotherapy **(8-11)**. There is level 1 evidence demonstrating OS benefit for pembrolizumab in the post-platinum setting compared to investigator's choice of chemotherapy of paclitaxel, docetaxel, or vinflunine **(8)**.

In May 2017, pembrolizumab and atezolizumab were granted accelerated approval for the first-line treatment of cisplatin-ineligible locally advanced or metastatic UC based on single-arm phase 2 studies demonstrating objective response rate (ORR) of 20%-25% and favorable toxicity profile **(13,14)**. In August 2018, based on early reviews of two ongoing phase 3 randomized

clinical trials (KEYNOTE-361 and IMvigor130), the FDA revised the first-line indications for pembrolizumab and atezolizumab, which are now indicated for patients who are ineligible for any platinum-containing chemotherapy, and patients who are cisplatin-ineligible and whose tumors express PD-L1. Importantly, studies to date consistently demonstrated durability of response and plateaus in the tails of survival curves (**Table 1**). In all of the above studies, PD-1 or PD-L1 inhibitors were administered until progressive disease or unacceptable toxicity.

Table 1: Summary of ICI response data in locally advanced or metastatic UC

	Phase	Objective response rate	Disease control rate	Median follow-up	Median duration of response	Reference
Pembrolizumab in 2L UC (KEYNOTE 045)	3	21%	38.5%	14 mo	Not reached (68% ≥ 1 year)	8
Pembrolizumab in 1L UC (KEYNOTE 052)	2	24%	34.0%	5 mo	Not reached (95% CI: 9mo – NR)	9
Atezolizumab in 1L UC	2	23%	30.0%	17.2 mo	Not reached (95% CI: 14.1mo – NR)	13
Avelumab in maintenance UC (JAVELIN Bladder 100)	3	9.7%	41.1%	>19 mo	Not reported	16

The phase 3 randomized clinical trials KEYNOTE-361 and IMvigor130 are exploring the upfront combination of platinum-containing chemotherapy with anti-PD-1 or anti-PD-L1 inhibition. Final PFS analysis of IMvigor130 reported that atezolizumab plus platinum/gemcitabine chemotherapy significantly improved PFS compared to placebo plus platinum/gemcitabine chemotherapy. Interim OS analysis favored atezolizumab plus platinum/gemcitabine chemotherapy over placebo plus platinum/gemcitabine chemotherapy; however, mature OS data are being awaited **(14)**. In contrast, the addition of pembrolizumab to platinum-containing chemotherapy for first-line treatment of advanced UC did not lead to statistically significant improvement in PFS or OS compared to chemotherapy alone in KEYNOTE-361 **(15)** It remains to be determined whether concurrent platinum-based chemotherapy plus immune checkpoint inhibition will become a standard of care for the first-line management of locally advanced or metastatic UC.

In January 2020, the phase 3 JAVELIN Bladder 100 trial was announced to have met its primary endpoint of OS at the planned interim analysis, which was subsequently published **(16).** In this study, patients with previously untreated locally advanced or metastatic UC whose disease did not progress on 4-6 cycles of induction platinum-containing chemotherapy were randomized to maintenance avelumab until progressive disease or intolerable toxicity plus best supportive care (BSC) or BSC alone. In April 2020, the FDA granted breakthrough therapy designation for avelumab for first-line maintenance treatment of locally advanced or metastatic UC.

1.3 Clinical data evaluating early ICI discontinuation

There is emerging clinical evidence that patients with various tumor histologies who stop ICI treatment earlier than anticipated may still derive benefit beyond treatment discontinuation. In a post-hoc analysis of CheckMate 069, a double-blind phase 2 study in which patients with treatment-naïve unresectable stage III or IV melanoma were randomized 2:1 to receive nivolumab plus ipilimumab followed by nivolumab maintenance versus placebo plus ipilimumab followed by placebo maintenance, 35 patients (37%) in the nivolumab plus ipilimumab arm discontinued treatment for treatment-related adverse events **(17)**. The median number of nivolumab and ipilimumab doses received in the patients who discontinued treatment

was each 3. At a minimum follow-up of 2 years, these 35 patients had similar objective ORR, disease progression rate, PFS and OS compared to the overall population randomized to nivolumab plus ipilimumab **(17)**.

In KEYNOTE-001, 61 advanced melanoma patients treated with pembrolizumab achieved complete response (CR) and stopped treatment at a median of 23 months. Of these patients, 59 (97%) maintained their CRs at a median off-treatment period of 10 months **(18)**. In the pivotal phase 3 KEYNOTE-006 study which demonstrated superiority of pembrolizumab over ipilimumab in advanced melanoma, patients who were randomized to the pembrolizumab arms (10mg/kg q2wk or 10mg/kg q3wk) continued treatment for up to 2 years or until disease progression or intolerable toxicity **(19)**. A total of 556 patients received pembrolizumab, 104 (19%) of whom completed 2 years of pembrolizumab. 102 (98%) of patients who completed 2 years of pembrolizumab were alive at a median of 9.7 months, and the median PFS was not reached **(20)**.

In a multicenter retrospective cohort of 19 metastatic renal cell carcinoma (RCC) patients treated with an anti-PD-1 or anti-PD-L1 antibody who achieved radiographic response and discontinued treatment for immune-related adverse events, 8 (42%) patients continued to have durable response and remained off treatment for a median of 20 months (range 7-72) **(21)**. More recently, a multicenter retrospective study of 20 patients with various advanced solid malignancies, including metastatic urothelial carcinoma, who discontinued anti-PD-1 or anti-PD-L1 inhibitor treatment after achieving SD, PR or CR demonstrated durable disease control after treatment discontinuation **(22)**.

Taken together, these data suggest that sustained clinical response can still be achieved with early treatment discontinuation. It is worthwhile to note that the only randomized prospective study to date that evaluated treatment duration of a PD1/PD-L1 inhibitor, CheckMate 153, challenged this concept **(23)**. In this study, patients with advanced or metastatic non-small cell lung cancer (NSCLC) who had received at least one prior systemic therapy and remained on treatment at 1 year were randomized to continue or stop nivolumab, regardless of response status at the time of randomization. When the subset of patients who had SD/PR/CR at randomization were evaluated for efficacy (163 of 220 randomized), PFS and OS were found to be longer for those who continued nivolumab. However, the study had several limitations. Patients with PD were included and randomized. Further, the primary endpoint of the study was incidence of high-grade AEs, and was not powered for efficacy analyses. Therefore, more definitive studies with careful patient selection and adequate statistical design are needed to answer the clinically important question of optimal duration of immune checkpoint inhibition.

2.0 OBJECTIVES

2.1 Primary Objective

To compare overall survival (OS)

2.2 Major Secondary Objectives

2.2.1 To compare progression free survival (PFS) by RECIST 1.1 criteria

2.2.2 To compare PFS by irRECIST criteria

2.2.3 To determine treatment-free interval (TFI) after ICI discontinuation (Arm B)

2.2.4 To determine the rate of response by RECIST 1.1 criteria after ICI rechallenge (Arm B)

2.2.5 To assess adverse events in each study arm by CTCAE 5.0

2.3 Biomarker Objectives

The following correlative study outline is provided to justify biospecimen collection. Investigators will submit correlative studies complete protocols including the correlative study objectives, endpoints, sample size, statistical analysis plan including power calculations, etc., once the clinical trial has completed at least 50% accrual and the correlative study appears feasible.

2.3.1 To evaluate archival tumor biomarkers associated with attaining an initial complete response (CR), partial response (PR), or SD (Arm A and B).

2.3.2 To evaluate archival tumor biomarkers associated with time to progression after ICI discontinuation and radiographic response after treatment rechallenge (Arm B)

2.3.3 To explore peripheral biomarkers associated with clinical outcomes (Arms A and B).

2.3.4 To evaluate baseline tumor-specific cell-free methylated DNA (cfMeDNA) and circulating tumor DNA (ctDNA) association with treatment-free interval (Arm B) and PFS (both arms separately and together).

2.3.5 To evaluate changes in tumor-specific cfMeDNA and ctDNA as a biomarker for early detection of disease progression prior to radiographic progression (Arm A and B).

2.3.6 To evaluate normal organ-specific cfMeDNA as a biomarker for early detection of immune-related adverse events (irAE) (Arm A and B).

2.4 Quality of Life (QOL) and Health Economics Objectives

2.4.1 To compare quality-adjusted survival using EQ-5D-5L (primary) and PROMIS PROPr (exploratory)

2.4.2 To compare global QOL using EORTC QLQ-C30

2.4.3 To compare patient-reported fatigue using PROMIS-Fatigue

2.4.4 To compare healthcare utilization

2.4.5 To compare incremental cost effectiveness and cost utility ratios

2.4.6 To compare financial toxicity

3.0 PATIENT SELECTION

For questions regarding eligibility criteria, see the Study Resources page. Please note that the Study Chair cannot grant waivers to eligibility requirements.

3.1 On-Study Guidelines

This clinical trial can fulfill its objectives only if patients appropriate for this trial are enrolled. All relevant medical and other considerations should be taken into account when deciding whether this protocol is appropriate for a particular patient. Physicians should consider the risks and benefits of any therapy, and therefore only enroll patients for whom this treatment is appropriate.

Physicians should consider whether any of the following may render the patient inappropriate for this protocol:

- Psychiatric illness which would prevent the patient from giving informed consent.
- Medical condition such as uncontrolled infection (including HIV), uncontrolled diabetes mellitus or cardiac disease which, in the opinion of the treating physician, would make this protocol unreasonably hazardous for the patient.
- Patients with a "currently active" second malignancy other than non-melanoma skin cancers or cervical carcinoma in situ. Patients are not considered to have a "currently active" malignancy if they have completed therapy and are free of disease for ≥ 2 years. Patients with NCCN very low or low risk prostate cancer on active surveillance without evidence of progression to higher risk disease for ≥ 2 years are allowed.

In addition:

- Women and men of reproductive potential should agree to use an appropriate method of birth control throughout their participation in this study due to the teratogenic potential of the therapy utilized in this trial. Appropriate methods of birth control include abstinence, oral contraceptives, implantable hormonal contraceptives or double barrier method (diaphragm plus condom).

3.2 Pre-registration Eligibility Criteria

Use the spaces provided to confirm a patient's eligibility by indicating Yes or No as appropriate. It is not required to complete or submit the following page(s).

When calculating days of tests and measurements, the day a test or measurement is done is considered Day 0. Therefore, if a test were done on a Monday, the Monday one week later would be considered Day 7.

A female of childbearing potential is a sexually mature female who: 1) has not undergone a hysterectomy or bilateral oophorectomy; or 2) has not been naturally postmenopausal for at least 12 consecutive months (i.e., has had menses at any time in the preceding 12 consecutive months).

___ 3.2.1 Documentation of Disease

Histologic Documentation: Histologically or cytologically confirmed urothelial carcinoma (UC) with predominantly transitional-cell features.

Stage: Locally advanced or metastatic disease prior to starting immune checkpoint blockade

Tumor Site: Bladder, renal pelvis, ureter, urethra, or prostate

___ **3.2.2 Patients must have received at least one cycle of current active treatment** with standard of care (SOC) FDA approved PD-1/L1 immune checkpoint inhibitor (ICI)-containing therapy for locally advance or metastatic UC.

___ **3.2.3 No history of tuberculosis, active hepatitis B (HBV) or hepatitis C (HCV), or uncontrolled human immunodeficiency virus (HIV)**

Patients with resolved HBV infection, defined as positive hepatitis B core antibody (anti-Hb) and negative hepatitis B surface antigen (HbsAg), are eligible.

Patients with positive HCV antibody are eligible if HCV RNA PCR is negative.

Patients with HIV who are compliant with highly active antiretroviral therapy (HAART) and have normal CD4 count and undetectable viral load are eligible.

___ **3.2.4 No history of allogeneic organ transplantation**

___ **3.2.5 No current immunosuppressive medication exceeding 10mg/day of prednisone or its equivalent**

Patients with pre-existing or treatment-emergent autoimmune or inflammatory disorders which do not require systemic immunosuppressive treatment exceeding 10mg/day of prednisone or its equivalent may be included.

___ **3.2.6 No female patients who are pregnant or breastfeeding, or male or female patients of reproductive potential who are not willing to employ effective birth control**, because this study involves investigational agents whose genotoxic, mutagenic, and teratogenic effects on the developing fetus and newborn are unknown. Therefore, for women of childbearing potential only, a negative urine or serum pregnancy test pregnancy test done ≤ 14 days prior to registration is required.

3.3 Registration Eligibility Criteria

___ **3.3.1** Patients without progressive disease per RECIST v 1.1 guidelines (i.e., with an ongoing CR, PR or SD) following completion of 12-18 months of ICI treatment.

___ **3.3.2** No toxicity from ICI therapy that makes continuation of treatment clinically unacceptable

___ **3.3.3** Adequate bone marrow and organ functions to continue PD-1/L1 ICI as judged by the treating physician

___ **3.3.4** Age ≥ 18 years

___ **3.3.5** ECOG Performance Status 0-2

___ **3.3.6** CNS metastasis is allowed if radiographically stable, clinically asymptomatic, and prior local therapy (if received) was completed > 6 months before registration

4.0 PATIENT REGISTRATION

4.1 Cancer Therapy Evaluation Program Investigator Registration Procedures

Food and Drug Administration (FDA) regulations and National Cancer Institute (NCI) policy require all individuals contributing to NCI-sponsored trials to register and renew their registration annually. To register, all individuals must obtain a Cancer Therapy Evaluation Program (CTEP) Identity and Access Management (IAM) account at [redacted] In addition, persons with a registration type of Investigator

(IVR), Non-Physician Investigator (NPIVR), or Associate Plus (AP) must complete their annual registration using CTEP's web-based Registration and Credential Repository (RCR) at [redacted]

RCR utilizes five person registration types.

- **IVR**—MD, DO, or international equivalent;
- **NPIVR**—advanced practice providers (e.g., NP or PA) or graduate level researchers (e.g., PhD);
- **AP**—clinical site staff (e.g., RN or CRA) with data entry access to CTSU applications such as the Roster Update Management System [RUMS], OPEN, Rave, acting as a primary site contact, or with consenting privileges;
- **Associate (A)—**other clinical site staff involved in the conduct of NCI-sponsored trials; and
- **Associate Basic (AB)**—individuals (e.g., pharmaceutical company employees) with limited access to NCI-supported systems.

RCR requires the following registration documents:

Documentation Required	IVR	NPIVR	AP	A	AB
FDA Form 1572	✓	✓			
Financial Disclosure Form	✓	✓	✓		
NCI Biosketch (education, training, employment, license, and certification)	✓	✓	✓		
GCP training	✓	✓	✓		
Agent Shipment Form (if applicable)	✓				
CV (optional)	✓	✓	✓		

An active CTEP-IAM user account and appropriate RCR registration is required to access all CTEP and Cancer Trials Support Unit (CTSU) websites and applications. In addition, IVRs and NPIVRs must list all clinical practice sites and Institutional Review Boards (IRBs) covering their practice sites on the FDA Form 1572 in RCR to allow the following:

- Addition to a site roster;
- Assign the treating, credit, consenting, or drug shipment (IVR only) tasks in OPEN;
- Act as the site-protocol Principal Investigator (PI) on the IRB approval; and
- Assign the Clinical Investigator (CI) role on the Delegation of Tasks Log (DTL).

In addition, all investigators acting as the Site-Protocol PI (investigator listed on the IRB approval), consenting/treating/drug shipment investigator in OPEN, or as the CI on the DTL must be rostered at the enrolling site with a participating organization.

Additional information is located on the CTEP website at [redacted] For questions, please contact the **RCR Help Desk** by email at [redacted]

Permission to view and download this protocol and its supporting documents is restricted and is based on person and site roster assignment housed in the CTSU Regulatory Support System (RSS).

4.2 CTSU Site Registration Procedures

This study is supported by the NCI Cancer Trials Support Unit (CTSU).

IRB Approval:

For CTEP and Division of Cancer Prevention (DCP) studies open to the National Clinical Trials Network (NCTN) and NCI Community Oncology Research Program (NCORP) Research Bases after March 1, 2019, all U.S.-based sites must be members of the NCI Central Institutional Review Board (NCI CIRB). In addition, U.S.-based sites must accept the NCI CIRB review to activate new studies at the site after March 1, 2019. Local IRB review will continue to be accepted for studies that are not reviewed by the CIRB, or if the study was previously open at the site under the local IRB. International sites should continue to submit Research Ethics Board (REB) approval to the CTSU Regulatory Office following country-specific regulations.

Sites participating with the NCI CIRB must submit the Study Specific Worksheet for Local Context (SSW) to the CIRB using IRBManager to indicate their intent to open the study locally. The NCI CIRB's approval of the SSW is automatically communicated to the CTSU Regulatory Office, but sites are required to contact the CTSU Regulatory Office at [redacted] to establish site preferences for applying NCI CIRB approvals across their Signatory Network. Site preferences can be set at the network or protocol level. Questions about establishing site preferences can be addressed to the CTSU Regulatory Office by email address or calling [redacted]

In addition, the Site-Protocol Principal Investigator (PI) (i.e. the investigator on the IRB/REB approval) must meet the following criteria in order for the processing of the IRB/REB approval record to be completed:

- Holds an active CTEP status;
- Rostered at the site on the IRB/REB approval (*applies to US and Canadian sites only*) and on at least one participating roster;
- If using NCI CIRB, rostered on the NCI CIRB Signatory record;
- Includes the IRB number of the IRB providing approval in the Form FDA 1572 in the RCR profile; and
- Holds the appropriate CTEP registration type for the protocol.

4.2.1 Additional site registration requirements

Additional requirements to obtain an approved site registration status include:

- An active Federal Wide Assurance (FWA) number;
- An active roster affiliation with the Lead Protocol Organization (LPO) or a Participating Organization (PO); and
- Compliance with all protocol-specific requirements (PSRs).

4.2.2 Downloading Site Registration Documents

Download the site registration forms from the protocol-specific page located on the CTSU members' website. Permission to view and download this protocol and its supporting documents is restricted based on person and site roster assignment. To participate, the institution and its associated investigators and staff must be associated with the LPO or a Protocol Organization (PO) on the protocol. One way to search for a protocol is listed below:

- Log in to the CTSU members' website [redacted] using your CTEP-IAM username and password;
- Click on *Protocols* in the upper left of the screen

  - Enter the protocol number in the search field at the top of the protocol tree, or

  - Click on the By Lead Organization folder to expand, then select *Alliance*, and NCI protocol number [*A031901*].
- Click on *Documents*, select *Site Registration*, and download and complete the forms provided. (Note: For sites under the CIRB, IRB data will load automatically to the CTSU.)

4.2.3 Submitting Regulatory Documents

Submit required forms and documents to the CTSU Regulatory Office using the Regulatory Submission Portal on the CTSU website.

To access the Regulatory Submission Portal log on to the CTSU members' website, go to the Regulatory section and select Regulatory Submission.

Institutions with patients waiting that are unable to use the Regulatory Submission Portal should alert the CTSU Regulatory Office immediately at 1-866-651-2878 in order to receive further instruction and support.

4.2.4 Checking your Site's Registration Status

Site's registration status may be verified on the CTSU members' website.

- Click on *Regulatory* at the top of the screen;
- Click on *Site Registration*; and
- Enter the site's 5-character CTEP Institution Code and click on Go.
  - Additional filters are available to sort by Protocol, Registration Status, Protocol Status, and/or IRB Type

Note: The status shown only reflects institutional compliance with site registration requirements as outlined within the protocol. It does not reflect compliance with protocol requirements for individuals participating on the protocol or the enrolling investigator's status with NCI or their affiliated networks.

4.3 Patient Pre-registration Requirements

Patients can be pre-registered to A031901 at any point after one cycle of therapy and at least one scan showing CR, PR, or SD. Patients with progressive disease may not be pre-registered. Patients who have received 12-18 months of immunotherapy therapy and meet both pre-registration and registration eligibility criteria may be pre-registered and registered at the same time.

4.3.1 Informed consent

The patient must be aware of the neoplastic nature of his/her disease and willingly consent after being informed of the procedure to be followed, the experimental nature of the therapy, alternatives, potential benefits, side-effects, risks, and discomforts. Current human protection committee approval of this protocol and a consent form is required prior to patient consent and registration.

Patients with impaired decision-making capacity may be enrolled on this study, where institutional policy and IRB of record allow.

4.4 Patient Registration Requirements

4.4.1 Informed consent

The patient must be aware of the neoplastic nature of his/her disease and willingly consent after being informed of the procedure to be followed, the experimental nature of the therapy, alternatives, potential benefits, side-effects, risks, and discomforts. Current human protection committee approval of this protocol and a consent form is required prior to patient consent and registration.

Patients with impaired decision-making capacity may be enrolled on this study, where institutional policy and IRB of record allow.

4.4.2 Patients will be registered to A031901 between 12-18 months after starting immune checkpoint inhibitor therapy.

4.4.3 Patient questionnaire booklets

Patient questionnaire booklets are to be ordered prior to the registration of any patients. Patient completed booklets can be ordered by downloading and completing the CTSU supply request form (located under the site registration documents section of the A031901 CTSU web site) and submitting it through the CTSU regulatory portal. Samples of the booklets are found in Appendix I, which are to be used for reference and IRB submission only. They are not to be used for patient completion.

4.5 Patient Pre-registration and Registration Procedures

The Oncology Patient Enrollment Network (OPEN) is a web-based registration system available on a 24/7 basis. OPEN is integrated with CTSU regulatory and roster data and with the LPOs registration/randomization systems or the Theradex Interactive Web Response System (IWRS) for retrieval of patient registration/randomization assignment. OPEN will populate the patient enrollment data in NCI's clinical data management system, Medidata Rave.

Requirements for OPEN access:

- A valid CTEP-IAM account;
- To perform enrollments or request slot reservations: Must be an LPO roster, ETCTN corresponding roster, or participating organization roster with the role of Registrar. Registrars must hold a minimum of an Associate Plus (AP) registration type;
- If a Delegation of Tasks Log (DTL) is required for the study, the registrars must hold the OPEN Registrar task on the DTL for the site; and
- Have an approved site registration for the protocol prior to patient enrollment.

To assign an Investigator (IVR) or Non-Physician Investigator (NPIVR) as the treating, crediting, consenting, drug shipment (IVR only), or receiving investigator for a patient transfer in OPEN, the IVR or NPIVR must list the IRB number used on the site's IRB approval on their Form FDA 1572 in RCR. If a DTL is required for the study, the IVR or NPIVR must be assigned the appropriate OPEN-related tasks on the DTL.

Prior to accessing OPEN, site staff should verify the following:

- Patient has met all eligibility criteria within the protocol stated timeframes; and

- All patients have signed an appropriate consent form and HIPAA authorization form (if applicable).

Note: The OPEN system will provide the site with a printable confirmation of registration and treatment information. You may print this confirmation for your records.

Access OPEN at [redacted] or from the OPEN link on the CTSU members' website. Further instructional information is in the OPEN section of the CTSU website at [redacted] For any additional questions, contact the CTSU Help Desk at [redacted]

4.6 Registration to Substudies and Companion Studies

4.6.1 Registration to substudies described in Section 14.0

There are two substudies within Alliance A031901. These studies must be offered to all patients registered to Alliance A031901 (although patients may opt to not participate). These substudies do not require separate IRB approval. The substudies included within Alliance A031901 are:

- Quality of Life and Health Economics Studies in A031901: Alliance A031901-HO1 (Section 14.1)
- Correlative Science Studies in A031901: Alliance A031901-ST1 (Section 14.2)

If a patient answers "yes" to "I choose to take part in the Quality of Life and Cost study and will fill out these forms," Question #1 in the model consent, they have consented to participate in the substudy described in Section 14.1. The patient should be registered to Alliance A031901-HO1 at the same time they are registered to the treatment trial (A031901). Questionnaires should be submitted per Section 6.4.

If a patient answers "yes" to "I agree that my samples and related information may be used for the laboratory studies described above," Question #2 in the model consent, they have consented to participate in the substudy described in Section 14.2. The patient should be registered to Alliance A031901-ST1 at the same time they are registered to the treatment trial (A031901). Samples should be submitted per Section 6.2.

4.7 Stratification Factors and Treatment Assignments for Registered Patients

4.7.1 Stratification Factors

Line and type of therapy:

- Chemotherapy followed by ICI maintenance
- ICI monotherapy first-line
- ICI monotherapy second-line and beyond

4.7.2 Treatment Assignments

The factors defined in Section 4.6.1 will be used as stratification factor.

After the patient has been registered into the study, the values of the stratification factor will be recorded, and the patient will be assigned to one of the following treatment groups using the Pocock and Simon dynamic allocation procedure which balances the marginal distributions of the stratification factor between the treatment groups.

1. Arm A: continuation of ICI treatment
2. Arm B: discontinuation of ICI treatment

5.0 STUDY CALENDAR

Pre-study Testing Intervals

The pre-study testing intervals are guidelines only. Laboratory and clinical parameters during treatment are to be followed using individual institutional guidelines and the best clinical judgment of the responsible physician. It is expected that patients on this study will be cared for by physicians experienced in the treatment and supportive care of patients on this trial.

When calculating days of tests and measurements, the day a test or measurement is done is considered Day 0. Therefore, if a test were done on a Monday, the Monday one week later would be considered Day 7.

To be completed ≤ 28 DAYS before registration: All laboratory studies, history and physical.

To be completed ≤ 42 DAYS before registration: Any X-ray, scan of any type or ultrasound which is utilized for tumor measurement per protocol

To be completed ≤ 60 DAYS before registration: Any baseline exams used for screening, or any X-ray, scan of any type or ultrasound of uninvolved organs which is not utilized for tumor measurement.

5.1 Arm A Study Calendar (For patients who are randomized to continue ICI treatment)

	Prior to Registration*	Every cycle (+/- 7 days)**	Post treatment follow up***
Tests & Observations			
History and physical, weight, ECOG PS	X	X	X
Height	X		
Vital signs (Pulse, BP, RR, O2 saturation)	X	X	X
Adverse Event Assessment	X	X	X
Registration Fatigue/Uniscale Assessment	X(1)		
Laboratory Studies			
Complete Blood Count, Differential, Platelets	X	X	X
Serum Creatinine,	X	X	X
Albumin, glucose	X	X	X
AST, ALT, Alk. Phos, Bili	X	X	X
TSH w/ reflex fT4 ‡	X	X	
Serum or Urine HCG	X(2)		
Staging			
Brain Imaging (MRI or CT)	A	A	A
CT/MRI chest/abd/pelvis	B(3)	B	B
Bone Scan	C	C	C
Correlative Studies: For those who consent to participate			
QOL/cost assessment	See Section 6.4.		
Tissue and Blood samples	See Section 6.2.		

* Labs completed prior to registration may be used for day 1 of cycle 1 tests if obtained ≤ 7 days prior to treatment. For subsequent cycles, labs, tests and observations may be obtained ≤ 48 hours prior to day of treatment.

** Cycle definition is based on ICI cycle length (see Section 7.2).

*** **For participants who progress**, **have started a new treatment, or have withdrawn consent:** Physical exam, laboratory, and imaging assessments are required within 4 weeks after the end of treatment. Thereafter, survival information is required every 6 months (± 4 weeks) until 5 years following registration, death, withdrawal of consent, or the end of the study, whichever occurs first. Survival information may be collected during clinic visit, phone, or medical record review.

For participants who discontinue treatment for reasons other than disease progression: Physical examination, laboratory, and imaging assessments are required every 12 weeks ± 4 weeks

until radiographic progression, initiation of new treatment, or up to 5 years following registration. Once a participant has progressed or initiated a new treatment, the participant will be followed for survival every 6 months (± 4 weeks) until 5 years following registration, death, withdrawal of consent, or the end of the study, whichever occurs first. Survival information may be collected during clinic visit, phone, or medical record review. See also Section 12.0.

‡ Free T4 will only be collected if TSH is abnormal, or if there is clinical suspicion of an AE related to the endocrine system.

1 To be completed after registration and prior to treatment.
2 For women of childbearing potential (see Section 3.3), obtain within ≤14 days prior to registration.
3 Baseline scans can include either: 1) a CT, spiral CT, or MRI, or 2) an FDG-PET scan and diagnostic CT. Both IV and oral contrast should be used unless contraindicated, with slide thickness of 5 mm or less. Supporting documentation is to be submitted, per Section 6.1.1.

A. Brain imaging is required only if there is indication of brain metastases at baseline or if signs or symptoms suggestive of brain metastases develop. Participants with a history of brain metastasis should have surveillance MRI with and without gadolinium contract approximately every 12 weeks (± 4 weeks), or sooner if clinically indicated.
B. Tumor assessments will occur every 12 weeks (± 4 weeks) until evidence of progression or relapse. The same imaging method should be used at screening/baseline. Confirmatory scans should also be obtained 4-8 weeks following documentation of objective progression when possible (see Section 11.0).
C. Bone scan is required only if there is indication of bone metastases at baseline or if signs or symptoms suggestive of bone metastases develop.

5.2 Arm B Study Calendar (for patients who are randomized to discontinue ICI treatment)

	Prior to Registration*	Clinical Monitoring**	Day 1 of Each cycle post-progression (Treatment rechallenge)**
Tests & Observations			
History and physical, weight, and ECOG PS	X	X	X
Height	X		
Vital signs (Pulse, BP, RR, O2 saturation)	X	X	X
Adverse Event Assessment	X	X	X
Registration Fatigue/Uniscale Assessment	X(1)		
Laboratory Studies			
Complete Blood Count, Differential, Platelets	X	X	X
Serum Creatinine	X	X	X
Albumin, Glucose	X	X	X
AST, ALT, Alk. Phos., Bili	X	X	X
Serum or Urine HCG	X(2)		
Staging			
Brain Imaging (MRI or CT)	A	A	A
CT/MRI chest/abd/pelvis	B (3)	B	B
Bone Scan	C	C	C
Correlative Studies: For those who consent to participate			
QOL/cost assessment	See Section 6.4.		
Tissue and Blood samples	See Section 6.2.		

* Labs completed prior to registration may be used for day 1 of cycle 1 tests if obtained ≤ 7 days prior to start of disease monitoring. For subsequent cycles during monitoring, labs, tests and observations may be obtained ≤ 72 hours prior to day of next cycle.

** **For participants who discontinue ICI treatment after randomization to Arm B:** Participants are required to undergo physical examination and imaging assessments every 12 weeks (± 4 weeks), from date of last scans, until evidence of progression or relapse. Labs and AE assessments are required every cycle (± 3 days); however, labs may be done with telephone call to review results within 48 hours of completion (without clinic visit), and AE assessments may be

done via telephone call. Once a participant has progressed, the ICI-containing treatment may be restarted at the discretion of the treating physician (see below; treatment rechallenge). Once a participant has progressed after treatment discontinuation and started a new treatment different from treatment rechallenge, they will be followed for survival every 6 months (± 4 weeks) until 5 years following registration, death, withdrawal of consent, or the end of the study, whichever occurs first. Survival information may be collected during clinic visit, phone, or medical record review.

For participants who progress after treatment discontinuation and restart ICI (treatment rechallenge): Participants who have received ICI monotherapy may be restarted on the same ICI treatment at the discretion of the treating physician. Participants who had received ICI maintenance treatment, either 4-6 cycles of platinum-containing chemotherapy followed by ICI maintenance if CR/SD/PD or ICI monotherapy may be restarted at the discretion of the treating physician. The interval between the scan showing disease progression and treatment rechallenge should be < 30 days if no confirmatory scan is obtained, or < 60 days if a confirmatory scan is obtained. During treatment rechallenge, labs, tests and observations may be obtained ≤ 48 hours prior to day of treatment. Physical examination and laboratory assessments are required every cycle until radiographic progression, initiation of new treatment, or up to 5 years following registration. Tumor assessments will occur every 12 weeks (± 4 weeks) until evidence of progression. Once a participant has progressed or initiated a new treatment after ICI rechallenge, the participant will be followed for survival every 6 months (± 4 weeks) until 5 years following registration, death, withdrawal of consent, or the end of the study, whichever occurs first. Survival information may be collected during clinic visit, phone, or medical record review.

For participants who start a treatment after ICI discontinuation without evidence of disease progression, or have withdrawn consent: Physical exam, laboratory, and imaging assessments are required within 4 weeks before starting the non-protocol treatment (including new treatment or resuming ICI treatment). Thereafter, survival information is required every 6 months (± 4 weeks) until 5 years following registration, death, withdrawal of consent, or the end of the study, whichever occurs first. Survival information may be collected during clinic visit, phone, or medical record review.

1 To be completed within 21 days after registration.

2 For women of childbearing potential (see Section 3.3), obtain within ≤ 14 days prior to registration.

3 Baseline scans can include either: 1) a CT, spiral CT, or MRI, or 2) an FDG-PET scan and diagnostic CT (with both IV and oral contrast unless contraindicated), and the CT acquired with 5 mm or less slice thickness. Supporting documentation is to be submitted, per Section 6.1.1

A Brain imaging is required only if there is an indication of brain metastases at baseline or if signs or symptoms suggestive of brain metastases develop. Participants with a history of brain metastasis should have surveillance MRI with and without gadolinium contract approximately every 12 weeks, or sooner if clinically indicated.

B Tumor assessments will occur every 12 weeks (± 4 weeks) until evidence of progression or relapse. The same imaging method should be used at screening/baseline. Confirmatory scans should also be obtained 4-8 weeks following documentation of objective progression when possible (see Section 11.0).

C Bone scan is required only if there is indication of bone metastases at baseline or if signs or symptoms suggestive of bone metastases develop.

6.0 DATA AND SPECIMEN SUBMISSION

6.1 Data Collection and Submission

6.1.1 Data submission schedule

A Data Submission Schedule (DSS) is available on the Alliance study webpage, within the Case Report Forms section. The data submission schedule is also available on the CTSU site within the study-specific case report forms folder.

6.1.2 Medidata Rave

Medidata Rave is a clinical data management system being used for data collection for this trial/study. Access to the trial in Rave is controlled through the CTEP-IAM system and role assignments.

Requirements to access Rave via iMedidata:

- A valid and active CTEP-IAM account; and
- Assigned a Rave role on the relevant LPO or PO roster at the enrolling site: Rave CRA, Rave Read Only, Rave CRA (LabAdmin), Rave SLA, or Rave Investigator.

  Rave role requirements:

  - Rave CRA or Rave CRA (Lab Admin) role must have a minimum of an Associate Plus (AP) registration type;
  - Rave Investigator role must be registered as a Non-Physician Investigator (NPIVR) or Investigator (IVR); and
  - Rave Read Only role must hold an Associates (A) registration type.

Refer to [redacted] for registration types and documentation required.

If the study has a Delegation of Tasks Log (DTL), individuals requiring write access to Rave must also be assigned the appropriate Rave tasks on the DTL.

Upon initial site registration approval for the study in Regulatory Support System (RSS), all persons with Rave roles assigned on the appropriate roster will be sent a study invitation e-mail from iMedidata. To accept the invitation, site staff must log in to the Select Login [redacted] using their CTEP-IAM username and password, and click on the accept link in the upper right-corner of the iMedidata page. Site staff will not be able to access the study in Rave until all required Medidata and study specific trainings are completed. Trainings will be in the form of electronic learnings (eLearnings), and can be accessed by clicking on the link in the upper right pane of the iMedidata screen. If an eLearning is required and has not yet been taken, the link to the eLearning will appear under the study name in iMedidata instead of the Rave EDC link; once the successful completion of the eLearning has been recorded, access to the study in Rave will be granted, and a Rave EDC link will display under the study name.

Site staff who have not previously activated their iMedidata/Rave account at the time of initial site registration approval for the study in RSS will also receive a separate invitation from iMedidata to activate their account. Account activation instructions are located on the CTSU website in the Rave section under the Rave resource materials (Medidata Account Activation and Study Invitation Acceptance). Additional information on iMedidata/Rave

is available on the CTSU members' website in the Data Management > Rave section at [redacted] or by contacting the CTSU Help Desk at [redacted] or by e-mail at [redacted]

6.1.3 Data Quality Portal

The Data Quality Portal (DQP) provides a central location for site staff to manage unanswered queries and form delinquencies, monitor data quality and timeliness, generate reports, and review metrics.

The DQP is located on the CTSU members' website under Data Management. The Rave Home section displays a table providing summary counts of Total Delinquencies and Total Queries. DQP Queries, DQP Delinquent Forms and the DQP Reports modules are available to access details and reports of unanswered queries, delinquent forms, and timeliness reports. Review the DQP modules on a regular basis to manage specified queries and delinquent forms.

The DQP is accessible by site staff that are rostered to a site and have access to the CTSU website. Staff that have Rave study access can access the Rave study data using a direct link on the DQP.

To learn more about DQP use and access, click on the Help icon displayed on the Rave Home, DQP Queries, and DQP Delinquent Forms modules.

Note: Some Rave protocols may not have delinquent form details or reports specified on the DQP. A protocol must have the Calendar functionality implemented in Rave by the Lead Protocol Organization (LPO) for delinquent form details and reports to be available on the DQP. Site staff should contact the LPO Data Manager for their protocol regarding questions about Rave Calendaring functionality.

6.1.4 Supporting documentation to be submitted to the Alliance

This study requires supporting documentation for diagnosis, treatment, response, and progression. Supporting documentation will include the following and must be submitted at the following time points:

- **Pathology report** documenting urothelial carcinoma (submit within 30 days following registration)
- **Progress notes or medication records** documenting systemic therapy for locally advanced or metastatic UC (submit within 30 days following registration)
- **Imaging reports and progress notes** corresponding to all submissions, including documentation of no evidence of progressive disease after completion of 12-18 months of ICI treatment (submit within 30 days following registration), disease response, and disease progression (submit within 30 days of event).

Supporting documentation is to be submitted via Medidata Rave.

6.2 Specimen collection and submission

The following correlative study outline is provided to justify biospecimen collection. Investigators will submit correlative studies complete protocols including the correlative study objectives, endpoints, sample size, statistical analysis plan including power calculations, etc., once the clinical trial has completed at least 50% accrual and the correlative study appears feasible.

The Alliance A031901 Correlative Science Manual (CSM) contains instructions for specimen collection, processing and shipping. The manual can be found on the BioMS and CTSU websites. Questions regarding the CSM should be address to the contacts specified in the manual.

For patients registered to substudy A031901-ST1: All participating institutions must ask patients for their consent to participate in the correlative substudies planned for Alliance A031901-ST1, although patient participation is optional. Biomarker studies will be performed. Rationale and methods for the scientific components of these studies are described in Section 14.0. For patients who consent to participate, tissue and blood will be collected at the following time points for these studies:

	After registration	**Week 12**	**At progression**
	For patients registered to A031901-ST1, submit the following:		
Paraffin block/cores of tumor tissue	X		
Plasma and buffy coat (EDTA/lavender top)	2 x 10 mL	2 x 10 mL	2 x 10 mL

6.3 Digital radiation therapy data submission using Transfer of Images and Data (TRIAD)

Transfer of Images and Data (TRIAD) is the American College of Radiology's (ACR) image exchange application. TRIAD provides sites participating in clinical trials a secure method to transmit images. TRIAD anonymizes and validates the images as they are transferred.

6.3.1 TRIAD Access Requirements

- A valid CTEP-IAM account.
- Registration and Credential Repository (RCR) registration type of: Associate (A), Associate Plus (AP), Non-Physician Investigator (NPIVR), or Investigator (IVR) registration type. Refer to the CTEP Registration Procedures section for instructions on how to request a CTEP-IAM account and complete registration in RCR.
- TRIAD Site User role on an NCTN or ETCTN roster.

All individuals on the Imaging and Radiation Oncology Core provider roster have access to TRIAD and may submit images for credentialing purposes, or for enrollments to which the provider is linked in OPEN.

6.3.2 TRIAD Installations

To submit images, the individual holding the TRIAD Site User role will need to install the TRIAD application on their workstation. TRIAD installation documentation is available at [redacted]

This process can be done in parallel to obtaining your CTEP-IAM account and RCR registration.

For questions, contact TRIAD Technical Support staff via email [redacted]

6.3.3 Image Submission

Data must be submitted according to the protocol requirements for ALL patients registered, whether or not assigned treatment is administered, including patients deemed to be ineligible.

DICOM tag dates and times cannot be altered prior to submission as they are used to put submissions into context regarding patient treatment.

Additional changes to DICOM tags prior to submission impede further technical analysis and should be avoided whenever possible.

DICOM images uploading is preferred to be submitted using TRIAD, however these methodologies are supported:

a) TRIAD-based (a PC with internet access and TRIAD software installation will be needed)

b) Web transfer-based (a PC with internet access and a web browser will be needed)

c) FTP transfer-based (a PC with internet access and any FTP software will be needed)

d) Mail/CD Shipment-based (only if electronic transfer approaches cannot be achieved)

Questions regarding image submissions can be send to [redacted]

Detailed Steps of Data Submission

Collection of images is required. Images will be collected digitally for central archiving and curation. Imaging studies will be collected digitally for the following time points:

1. Pre-study
    a. Every effort should be made to deposit pre-ICI and post-ICI radiological assessments (e.g. CT, MRI, FDG-PET, bone scan, and/or MRI/CT brain).
        i. Pre-ICI scans consist of scans performed immediately prior to initiation of ICI therapy.
        ii. Post-ICI scans consist of scans performed after initiation of ICI therapy, during the 12-18 months of treatment prior to study screening.
2. Baseline
    a. CT, spiral CT, or MRI, OR FDG-PET scan and diagnostic CT of the chest/abdomen/pelvis
        i. Requires IV and oral contrast unless contraindicated
        ii. Requires 5mm slice thickness for the CT
    b. MRI or CT of the brain
        i. Required if there is an indication of brain metastases at baseline or if signs or symptoms suggestive of brain metastases develop
        ii. Required if patients have a history of brain metastases
        iii. Requires sequences done with and without gadolinium contrast unless contraindicated
    c. Bone scan of the whole body
        i. Required only if there is an indication of bone metastases at baseline or if signs or symptoms suggestive of bone metastases develop
3. Restaging
    a. Same chest/abdomen/pelvis imaging as acquired at baseline

   b. Same brain imaging as acquired at baseline or if signs/symptoms suggestive of metastases develop
   c. Same bone imaging as acquired at baseline or if signs/symptoms suggestive of metastases develop
4. Progression after randomization (Arm A and B) and Progression after ICI rechallenge (Arm B only)
5. Rechallenge restaging (Arm B only)
   a. Same chest/abdomen/pelvis imaging as acquired at baseline
   b. Same brain imaging as acquired at baseline or if signs/symptoms suggestive of metastases develop
   c. Same bone imaging as acquired at baseline or if signs/symptoms suggestive of metastases develop
6. Rechallenge progression (Arm B only)

The complete imaging data set in digital DICOM format will be submitted electronically to the Imaging and Radiation Oncology Core at Ohio (IROC Ohio) within no more than 3 business days upon the image acquisition completeness. BMP files, JPG files, or hard copies (films) are not acceptable. The raw data of the entire study should be saved until the imaging data is accepted by IROC Ohio

Sites need to de-identify the patient data using institutional procedures to remove patient name and medical record number while preserving the Alliance patient ID number (e.g., 112136) and protocol number (e.g., ALLIANCE031901), respectively.

DICOM tag dates and times cannot be altered prior to submission as they are used to put submissions into context regarding patient treatment.

Additional changes to DICOM tags prior to submission impede further technical analysis and should be avoided whenever possible.

Imaging data should be submitted electronically to IROC Ohio via TRIAD, Web Transfer or FTP Transfer:

1. TRIAD based data transfer
   The standard TRIAD based data transfer approach will be provided separately through IROC efforts via the specific trial e-mail [redacted] per the request by participating sites before their first data submission.
2. Web Transfer
   [redacted]
   Any PCs with internet access and web browser (e.g., Chrome, Edge, Internet Explorer, Mozilla Firefox) can be used to web transfer DICOM images and other required files to IROC Ohio. The standard Web Transfer information will be provided separately through the specific trial e-mail [redacted] per the request by participating sites before their first data submission.
3. FTP Transfer
   Any FTP software can be used to initiate access to the secure FTP Server of IROC Ohio. The standard FTP access information will be provided separately through the specific trial e-mail [redacted] per the request by participating sites before their first data submission.
4. Mail/CD Shipment
   Only if electronic data transfer approaches cannot be achieved, the de-identified images in digital DICOM format can be burned to a CD and mailed to IROC Ohio. Submit only one patient's images per CD, with the patient's Alliance ID number, study type, date of

scans, and name of submitting institution.

Submit these data to:

[redacted]

Once the imaging data submission is done, send an e-mail to IROC Ohio at the specific trial email [redacted] to inform that the study has been submitted from the institution. IROC Ohio will notify site and ALLIANCE A031901 imaging committee within 2 business days of the data receipt, and then, within 3 business days following the data receipt, of the quality check report.

Any questions or problems about the data submission to IROC Ohio email [redacted] for help.

6.4 Submission of Patient Completed Measures

Patient-completed questionnaire booklets for this study are to be ordered prior to the registration of any patients (see Section 4.3). Samples of questionnaire booklets are available in Appendix II for reference and IRB submission only. They are not to be used for patient completion. Booklets must be given to patients to complete and patients should be instructed to return the booklets to site staff either in person or by mail and site staff will enter patient responses into Medidata Rave. The booklets should be completed within a +/- 2 week window at each time point. At visits in which booklets are to be completed, the booklet should be given to the patient before any discussion of the patient's health status or test results. Booklet administration schedule is provided below.

Form	At registration	6 months	12 months	18 months	24 months
For patients registered to A031901-HO1, submit patient-completed questionnaires* at the following time points:					
EQ-5D-5L	X	X	X	X	X
EORTC QLQ-C30	X	X	X	X	X
PROMIS-29+2 v2.1 (PROPr) (includes PROMIS-Fatigue)	X	X	X	X	X
Healthcare Utilization	X	X	X	X	X
COST-FACIT	X	X	X	X	X

* See Appendix I for the EQ-5D-5L, EORTC QLQ-C30, PROMIS-29+2 v2.1 (PROPr), healthcare utilization and COST-FACIT questionnaires for IRB submission and review only. Note that the PROMIS-Fatigue is embedded within the PROMIS-29+2 v2.1 (PROPr). Patients must complete the questionnaires in booklet format.

The forms may be completed in person in the clinic or remotely via telephone calls with the patient.

Verbal administration of the measures for visually impaired patients is permitted if the measure and verbal administration of the measure is conducted in a language understandable to the patients.

6.4.1 Patient Language Considerations

All of the QOL and healthcare utilization measures are available in both English and Spanish. Patients not speaking one of those languages should not be registered to the A031901 HO-1 substudy.

7.0 TREATMENT PLAN/INTERVENTION

Protocol treatment is to begin ≤ 7 days of registration.

For questions regarding treatment, please see the study contacts page.

7.1 Protocol Therapy

This is a randomized trial. Patients will be randomized to continuing PD-1/L1 ICI treatment vs discontinuing ICI. Patients should continue ICI treatment during study screening.

Patients randomized to Arm A will continue to receive ICI. Following randomization, the next dose of ICI should be administered based on the cycle length of ICI they are receiving. For example, a patient receiving pembrolizumab (cycle length = 21 days) randomized to Arm A on 4/01/2021 whose last dose of pembrolizumab was administered on 3/15/21 should receive the next cycle of pembrolizumab on 4/05/2021 (+/- 3 days).

At disease progression patient should be treated at the discretion of the treating physician.

Patients randomized to Arm B will discontinue treatment with the ICI. Following randomization to Arm B, the last dose of ICI should be administered within 1 cycle length of randomization. For example, a patient receiving pembrolizumab (cycle length = 21 days) randomized to Arm B on 4/01/21 should receive their last dose of pembrolizumab between 3/11/21 and 4/22/21.

At disease progression patients will have the option to restart ICI-containing treatment.

For questions regarding treatment, please see the study contacts page.

7.2 ICI choices

The following applies to all ICI choices:

- A +/- 3 day treatment window
- Treatment may be delayed for up to a maximum of 8 week from the last dose. A dose will be considered delayed if the delay is exceeding 3 days (i.e., ≥ 4 days from scheduled dosing date). The reason for the dose delay will be captured on the treatment forms.

Investigators will choose one of the below ICI treatments for the duration of the trial. The following rules apply:

- **Pembrolizumab (Cycle = 21 or 42 days):** To be administered by IV over 30 minutes at 200 mg every 21 days OR at 400 mg every 42 days.
- **Nivolumab (Cycle = 28 days):** To be administered by IV over 30 minutes at 240 mg every 14 days or 480 mg every 28 days.
- **Atezolizumab (Cycle = 21 days)**: To be administered by IV at 1200 mg every 21 days. The first infusion should be given over 60 minutes, if tolerated well, subsequent infusions may be given over 30 minutes.

- **Avelumab (Cycle = 28 days):** To be administered by IV over 60 minutes at 800 mg every 14 days. Premedication is not required but may be administered based upon clinical judgement and presence/severity of prior infusion reactions.

8.0 DOSE AND TREATMENT MODIFICATIONS

8.1 Ancillary Therapy, Concomitant Medications, and Supportive Care

8.1.1 Patients should not receive any other systemic treatment which would be considered treatment for the primary neoplasm or impact the primary endpoint.

8.1.2 Patients should receive full supportive care while on this study.

This includes blood product support, antibiotic treatment, and treatment of other newly diagnosed or concurrent medical conditions. All blood products and concomitant medications such as antidiarrheals, analgesics, and/or antiemetics received from the first day of study treatment administration until 30 days after the final dose will be recorded in the medical records.

Suggested supportive care measures for the management of AEs with potential immunologic etiology are outlined in Section 8.2. Where appropriate, these guidelines include the use of oral or IV treatment with corticosteroids as well as additional anti-inflammatory agents if symptoms do not improve with administration of corticosteroids. Several courses of steroid tapering may be necessary as symptoms may worsen when the steroid dose is decreased. For each disorder, attempts should be made to rule out other causes such as metastatic disease or bacterial or viral infection, which may require additional supportive care.

8.1.3 Treatment with hormones or other chemotherapeutic agents may not be administered except for steroids given for immune-related toxicities (e.g., colitis); hormones administered for non-disease-related conditions (e.g., insulin for diabetes); premedication for hypersensitivity reactions (e.g., premedication for iodinated contrast allergy before CT scan) and intermittent use of dexamethasone as an antiemetic.

8.1.4 Antiemetics may be used at the discretion of the attending physician, except for the steroids above.

8.1.5 Palliative radiation therapy during protocol therapy may be administered. Patients who receive palliative radiation but otherwise do not have evidence of disease progression are allowed to remain on protocol until evidence of radiographic progression. Patients randomized to Arm A may continue ICI, and patients randomized to Arm B my remain off ICI until progression. Decision to hold ICI during palliative radiation is at the discretion of the treating physician.

8.1.6 Alliance Policy Concerning the Use of Growth Factors

Blood products and growth factors should be utilized as clinically warranted and following institutional policies and recommendations. The use of growth factors should follow published guidelines of the American Society of Clinical Oncology Clinical Practice Guideline Update. J Clin Oncol 33: 3199-3212, 2015 and American Society of Clinical Oncology – American Society of Hematology Clinical Practice Guideline Update on the Use of Epoetin and Darbepoetin in Adult Patients with Cancer. J Clin Oncol 28:4996-5010, 2010.

8.1.7 Hypersensitivity/infusion reactions

Treat hypersensitivity and infusion reactions to study treatment per institutional standards.

8.2 Dose Modifications

For patients randomized to ICI treatment continuation in Arm A and patients who progress after treatment discontinuation and subsequently undergo treatment rechallenge in Arm B, dose interruptions are permitted. However, dose reductions and escalations are not allowed.

Dosing interruptions are permitted in the case of medical/surgical events or logistical reasons not related to study therapy (e.g., elective surgery, unrelated medical events, patient vacation, and/or holidays). Patients should be placed back on study therapy within 1-cycle length of the scheduled interruption (e.g., 3 weeks for pembrolizumab 200mg Q3W). The reason for interruption should be documented in the patient's study record.

Adverse events associated with PD-1/L1 inhibitors may represent an immunologic etiology. These AEs may occur shortly after the first dose or several months after the last dose of treatment (i.e. after treatment discontinuation). In general, the approach to suspected treatment-related AEs is similar across different PD-1/L1 agents as well as any involved organ system. Subjects should have a thorough diagnostic work-up to evaluate potential drug- and non-drug-related diagnoses. For suspected ICI-related AEs, based on the severity of the event, management with immunosuppressants may be necessary. In general, dose delays (for patients on active treatment) and observation are adequate for low-grade AEs. For moderate- and high-grade AEs, immunosuppression with corticosteroids should be utilized. Once the AE has begun to improve, corticosteroids can be tapered over approximately 3 weeks to 6 weeks (depending on the severity of the AE). Safety management algorithms for organ-specific AEs are found below to serve as general guidance.

AER reporting may be required for some adverse events (See Section 9.0)

8.2.1 Dose Modification and Supportive Care Guidelines for PD-1/L1 ICI-related Adverse Events

Adverse events (both nonserious and serious) associated with pembrolizumab exposure may represent an immunologic etiology. These AEs may occur shortly after the first dose or several months after the last dose of treatment. Pembrolizumab must be withheld for drug-related toxicities and severe or life-threatening AEs as described in this section.

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

Patients should receive appropriate supportive care measures as deemed necessary by the treating investigator. Suggested supportive care measures for the management of AEs with potential immunologic etiology are also outlined in the table in this section. Where appropriate, these guidelines include the use of oral or IV treatment with corticosteroids as well as additional anti-inflammatory agents if symptoms do not improve with administration of corticosteroids. Note that several courses of steroid tapering may be necessary as symptoms may worsen when the steroid dose is decreased. For each disorder, attempts should be made to rule out other causes such as metastatic disease or bacterial or viral infection, which might require additional supportive care. The treatment guidelines

are intended to be applied when the investigator determines the events to be related to pembrolizumab.

Note: If after the evaluation the event is determined not to be related, the investigator does not need to follow the treatment guidance (as outlined below).

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

Clinicians should refer to the package insert for further guidance on specific drug dose modifications.

Table: Dose Modification and Toxicity Management Guidelines for Immune-related AEs and Infusion Reactions Associated with Pembrolizumab

General instructions:

1. For non-endocrine-related severe and life-threatening irAEs, investigators should consider the use of IV corticosteroids followed by oral steroids. Other immunosuppressive treatment should begin if the irAEs are not controlled by corticosteroids. Some non-endocrine irAEs do not require steroids. For example, celiac disease induced by pembrolizumab can be controlled by diet alone.
2. For non-endocrine-related toxicities, pembrolizumab must be permanently discontinued if the irAE does not resolve or the corticosteroid dose is not ≤10 mg/day within 12 weeks of the last pembrolizumab-treatment.
3. Generally, when corticosteroids are used, investigators should begin a taper when the irAE is ≤Grade 1 and continue at least 4 weeks.
4. If pembrolizumab has been withheld due to a non-endocrine irAE, pembrolizumab may generally resume after the irAE has decreased to ≤Grade 1 after a corticosteroid taper.

irAEs	**Toxicity grade (CTCAE V5.0)**	**Action with pembrolizumab**	**Corticosteroid and/or other therapies**	**Monitoring and follow-up**
Pneumonitis	Grade 2	Withhold	Administer corticosteroids (initial dose of 1 to 2 mg/kg prednisone or equivalent) followed by taper Add prophylactic antibiotics for opportunistic infections	Monitor participants for signs and symptoms of pneumonitis Evaluate participants with suspected pneumonitis with radiographic imaging and initiate corticosteroid treatment
	Recurrent Grade 2, Grade 3 or 4	Permanently discontinue		

Diarrhea / Colitis	Grade 2 or 3	Withhold	Administer corticosteroids (initial dose of 1 to 2 mg/kg prednisone or equivalent) followed by taper Patients who do not respond to corticosteroids should be seen by a gastroenterologist for confirmation of the diagnosis and consideration of secondary immune suppression	Monitor participants for signs and symptoms of enterocolitis (*i.e.*, diarrhea, abdominal pain, blood or mucus in stool with or without fever) and of bowel perforation (*i.e.* peritoneal signs and ileus) Specifically assess for celiac disease serologically, and exclude *Clostridium difficile* infection Participants with ≥Grade 2 diarrhea suspecting enterocolitis should consider GI consultation and performing endoscopy to rule out enterocolitis and assess mucosal severity 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
	Recurrent Grade 3 or Grade 4	Permanently discontinue		

AST or ALT elevation or Increased Bilirubin	Grade 2 [a]	Withhold	Administer corticosteroids (initial dose of 0.5 to 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 [b] or 4 [c]	Permanently discontinue	Administer corticosteroids (initial dose of 1 to 2 mg/kg prednisone or equivalent) followed by taper	

Type 1 diabetes mellitus (T1DM) or Hyperglycemia	Grade 1 or 2	Continue		Investigate for diabetes. In the absence of corticosteroids or diabetes medication non-adherence, any grade hyperglycemia may be an indication of beta-cell destruction and pembrolizumab-induced diabetes akin to type 1 diabetes. This should be treated as a Grade 3 event. Given this risk, exercise caution in utilizing non-insulin hypoglycemic agents in this setting. After a thorough investigation of other potential causes, which may involve a referral to an endocrinologist, follow institutional guidelines. Monitor glucose control.

	New onset T1DM (evidence of β-cell failure) or Grade 3 or 4 hyperglycemia	Withhold [d] Resume pembrolizumab when symptoms resolve and glucose levels are stable	Initiate treatment with insulin If patient is found to have diabetic ketoacidosis or hyperglycemic hyperosmolar syndrome, treat as per institutional guidelines with appropriate management and laboratory values (*e.g.* anion gap, ketones, blood pH, *etc*.) reported	Monitor for glucose control Strongly consider referral to endocrinologist Obtain C-peptide level paired with glucose, autoantibody levels (*e.g.* GAD65, islet cell autoantibodies), and hemoglobin A1C level
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) Provide adrenal insufficiency precautions including indications for stress dose steroids and medical alert jewelry Strongly consider referral to endocrinologist
	Grade 3 or 4	Withhold or permanently discontinue [d]		
Hyperthyroidism	Grade 2	Consider withholding. Resume pembrolizumab when symptoms are controlled, and thyroid function is improving	Treat with nonselective beta-blockers (*e.g.*, propranolol) or thionamides as appropriate Initiate treatment with anti-thyroid drug such as methimazole or	Monitor for signs and symptoms of thyroid disorders Strongly consider referral to endocrinologist

	Grade 3 or 4	Withhold or permanently discontinue [d]	carbimazole as needed	
Hypothyroidism	Grade 2, 3 or 4	Continue	Initiate thyroid replacement hormones (*e.g.*, levothyroxine or liothyronine) per standard of care	Monitor for signs and symptoms of thyroid disorders
Nephritis: grading according to increased creatinine or acute kidney injury	Grade 2	Withhold	Administer corticosteroids (prednisone 1 to 2 mg/kg or equivalent) followed by taper	Monitor changes of renal function Strongly consider referral to nephrologist
	Grade 3 or 4	Permanently discontinue		
Cardiac Events (including myocarditis, pericarditis, arrhythmias, impaired ventricular function, vasculitis)	Asymptomatic cardiac enzyme elevation with clinical suspicion of myocarditis (previously CTCAE v4.0 Grade 1), or Grade 1	Withhold	Based on severity of AE administer corticosteroids	Ensure adequate evaluation to confirm etiology and/or exclude other causes Strongly consider referral to cardiologist and cardiac MRI Consider endomyocardial biopsy If event resolves to Grade 1 or better, taper corticosteroids over ≥1 month

	Grade 2, 3 or 4	Permanently discontinue	Initiate treatment with corticosteroids equivalent to 1-2 mg/kg/day IV methylprednisolone and convert to 1-2 mg/kg/day oral prednisone or equivalent upon improvement If event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent Initiate treatment per institutional guidelines and consider antiarrhythmic drugs, temporary pacemaker, extracorporeal membrane oxygenation (ECMO), ventricular assist device (VAD), or pericardiocentesis as appropriate	Ensure adequate evaluation to confirm etiology and/or exclude other causes Strongly consider referral to cardiologist and cardiac MRI Consider endomyocardial biopsy If event resolves to Grade 1 or better, taper corticosteroids over ≥1 month
Exfoliative Dermatologic Conditions	Suspected SJS, TEN, or DRESS	Withhold	Based on severity of AE administer corticosteroids	Ensure adequate evaluation to confirm etiology or exclude other causes Strongly consider referral to dermatologist Consider skin biopsy for evaluation of etiology
	Confirmed SJS, TEN, or DRESS	Permanently discontinue		
All Other irAEs	Persistent Grade 2	Withhold		Ensure adequate evaluation to

	Grade 3	Withhold or discontinue based on the event [e]	Based on severity of AE administer corticosteroids	confirm etiology or exclude other causes
	Recurrent Grade 3 or Grade 4	Permanently discontinue		

Infusion-Related Reactions

Infusion Reactions	**NCI CTCAE Grade**	**Treatment**	**Premedication at subsequent dosing**
Mild reaction; infusion interruption not indicated; intervention not indicated	Grade 1	Increase monitoring of vital signs as medically indicated until the participant is deemed medically stable in the opinion of the investigator.	None

Infusion Reactions	NCI CTCAE Grade	Treatment	Premedication at subsequent dosing
Requires therapy or infusion interruption but responds promptly to symptomatic treatment (*e.g.*, antihistamines, NSAIDs, narcotics, IV fluids); prophylactic medications indicated for ≤24 hrs.	Grade 2	• **Stop Infusion.** • Additional appropriate medical therapy may include but is not limited to: • IV fluids • Antihistamines • NSAIDs • Acetaminophen • Narcotics • Increase monitoring of vital signs as medically indicated until the participant is deemed medically stable in the opinion of the investigator. • If symptoms resolve within 1 hour of stopping drug infusion, the infusion may be restarted at 50% of the original infusion rate (*e.g.* from 100 mL/hr. to 50 mL/hr.). Otherwise dosing will be held until symptoms resolve and the participant should be premedicated for the next scheduled dose. **Participants who develop Grade 2 toxicity despite adequate premedication should be permanently discontinued from further study drug treatment**	Participant may be premedicated 1.5h (± 30 minutes) prior to infusion of study intervention with: Diphenhydramine 50 mg PO (or equivalent dose of antihistamine). Acetaminophen 500-1000 mg PO (or equivalent dose of analgesic).

Infusion Reactions	NCI CTCAE Grade	Treatment	Premedication at subsequent dosing
Prolonged (*i.e.*, not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for other clinical sequelae (e.g., renal impairment, pulmonary infiltrates)	Grade 3	• **Stop Infusion.** • Additional appropriate medical therapy may include but is not limited to: • Epinephrine** • IV fluids • Antihistamines • NSAIDs • Acetaminophen • Narcotics • Oxygen • Pressors • Corticosteroids (*e.g.* methylprednisolone 2 mg/kg/day or dexamethasone 10 mg every 6 hours) • Increase monitoring of vital signs as medically indicated until the participant is deemed medically stable in the opinion of the investigator. • Hospitalization may be indicated. **In cases of anaphylaxis, epinephrine should be used immediately. Participant is permanently discontinued from further study drug treatment.	No subsequent dosing.
Life-threatening; pressor or ventilator support indicated	Grade 4	Admit participant to intensive care unit (ICU) and initiate hemodynamic monitoring, mechanical ventilation, and/or IV fluids and vasopressors as needed. Monitor other organ function closely. Manage constitutional symptoms and organ toxicities as per institutional practice. Follow Grade 3 recommendations as applicable.	No subsequent dosing.

Infusion Reactions	NCI CTCAE Grade	Treatment	Premedication at subsequent dosing

AE(s)=adverse event(s); ALT= alanine aminotransferase; AST=aspartate aminotransferase; CTCAE=Common Terminology Criteria for Adverse Events; DRESS=Drug Rash with Eosinophilia and Systemic Symptom; ECMO=extracorporeal membrane oxygenation; GI=gastrointestinal; ICU=intensive care unit; IO=immuno-oncology; ir=immune related; IV=intravenous; MRI=magnetic resonance imaging; PO=per os; SJS=Stevens-Johnson Syndrome; T1DM=type 1 diabetes mellitus; TEN=Toxic Epidermal Necrolysis; ULN=upper limit of normal; VAD=ventricular assist device.

Note: Non-irAE will be managed as appropriate, following clinical practice recommendations.

[a] AST/ALT: >3.0 to 5.0 x ULN if baseline normal; >3.0 to 5.0 x baseline, if baseline abnormal; bilirubin:>1.5 to 3.0 x ULN if baseline normal; >1.5 to 3.0 x baseline if baseline abnormal

[b] AST/ALT: >5.0 to 20.0 x ULN, if baseline normal; >5.0 to 20.0 x baseline, if baseline abnormal; bilirubin:>3.0 to 10.0 x ULN if baseline normal; >3.0 to 10.0 x baseline if baseline abnormal

[c] AST/ALT: >20.0 x ULN, if baseline normal; >20.0 x baseline, if baseline abnormal; bilirubin: >10.0 x ULN if baseline normal; >10.0 x baseline if baseline abnormal

[d] The decision to withhold or permanently discontinue pembrolizumab is at the discretion of the investigator or treating physician. If control achieved or ≤Grade 2, pembrolizumab may be resumed.

[e] Events that require discontinuation include but are not limited to: encephalitis and other clinically important irAEs (*e.g.* vasculitis and sclerosing cholangitis).

Appropriate resuscitation equipment should be available at the bedside and a physician readily available during the period of drug administration. For further information, please refer to the Common Terminology Criteria for Adverse Events v5.0 (CTCAE) at [redacted]

Neurological Toxicities

Event	Management
Immune-mediated neuropathy, Grade 1	• Continue pembrolizumab. • Investigate etiology. • Any cranial nerve disorder (including facial paresis) should be managed as per Grade 2 management guidelines below.

Immune-mediated neuropathy, including facial paresis, Grade 2	• Withhold pembrolizumab for up to 12 weeks after event onset. [a]
	• Investigate etiology and refer patient to neurologist.
	• Initiate treatment as per institutional guidelines.
	• For general immune-mediated neuropathy:
	  o If event resolves to Grade 1 or better, resume pembrolizumab. [b]
	  o If event does not resolve to Grade 1 or better while withholding pembrolizumab, permanently discontinue pembrolizumab. [c]
	• For facial paresis:
	  o If event resolves fully, resume pembrolizumab. [b]
	  o If event does not resolve fully while withholding pembrolizumab, permanently discontinue pembrolizumab. [c]

Immune-mediated neuropathy, including facial paresis, Grade 3 or 4	• Permanently discontinue pembrolizumab. [c] • Refer patient to neurologist. • Initiate treatment as per institutional guidelines.
Myasthenia gravis and Guillain-Barré syndrome (any grade)	• Permanently discontinue pembrolizumab. [c] • Refer patient to neurologist. • Initiate treatment as per institutional guidelines. • Consider initiation of corticosteroids equivalent to 1–2 mg/kg/day oral or IV prednisone.

[a] Pembrolizumab may be withheld for a longer period of time (*i.e.*, >12 weeks after event onset) to allow for corticosteroids (if initiated) to be reduced to the equivalent of ≤10 mg/day oral prednisone. The acceptable length of the extended period of time must be based on an assessment of benefit–risk by the investigator and in alignment with the protocol requirements for the duration of treatment and documented by the investigator.
[b] If corticosteroids have been initiated, they must be tapered over ≥1 month to the equivalent of ≤10 mg/day oral prednisone before pembrolizumab can be resumed.
[c] Resumption of pembrolizumab may be considered in patients who are deriving benefit and have fully recovered from the immune-mediated event. The decision to re-challenge patients with pembrolizumab should be based on investigator's assessment of benefit–risk and documented by the investigator (or an appropriate delegate).

Event	Management
Immune-mediated myelitis, Grade 1	• Continue pembrolizumab unless symptoms worsen or do not improve. • Investigate etiology and refer patient to a neurologist.
Immune-mediated myelitis, Grade 2	• Permanently discontinue pembrolizumab. • Investigate etiology and refer patient to a neurologist. • Rule out infection. • Initiate treatment with corticosteroids equivalent to 1-2 mg/kg/day oral prednisone.
Immune-mediated myelitis, Grade 3 or 4	• Permanently discontinue pembrolizumab. • Refer patient to a neurologist. • Initiate treatment as per institutional guidelines.

Event	Management
Immune-mediated meningoencephalitis, all grades	• Permanently discontinue pembrolizumab. [a] • Refer patient to neurologist. • Initiate treatment with corticosteroids equivalent to 1–2 mg/kg/day IV methylprednisolone and convert to 1–2 mg/kg/day oral prednisone or equivalent upon improvement. • If event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent. • If event resolves to Grade 1 or better, taper corticosteroids over ≥1 month.

[a] Resumption of pembrolizumab may be considered in patients who are deriving benefit and have fully recovered from the immune-mediated event. The decision to re-challenge patients with pembrolizumab should be based on investigator's assessment of benefit–risk and documented by the investigator (or an appropriate delegate).

Neurological Toxicities

Event	Management
Immune-mediated neuropathy, Grade 1	• Continue pembrolizumab. • Investigate etiology. • Any cranial nerve disorder (including facial paresis) should be managed as per Grade 2 management guidelines below.
Immune-mediated neuropathy, including facial paresis, Grade 2	• Withhold pembrolizumab for up to 12 weeks after event onset. [a] • Investigate etiology and refer patient to neurologist. • Initiate treatment as per institutional guidelines. • For general immune-mediated neuropathy: o If event resolves to Grade 1 or better, resume pembrolizumab. [b] o If event does not resolve to Grade 1 or better while withholding pembrolizumab, permanently discontinue pembrolizumab. [c] • For facial paresis: o If event resolves fully, resume pembrolizumab. [b] o If event does not resolve fully while withholding pembrolizumab, permanently discontinue pembrolizumab. [c]
Immune-mediated neuropathy, including facial paresis, Grade 3 or 4	• Permanently discontinue pembrolizumab. [c] • Refer patient to neurologist. • Initiate treatment as per institutional guidelines.
Myasthenia gravis and Guillain-Barré syndrome (any grade)	• Permanently discontinue pembrolizumab. [c] • Refer patient to neurologist. • Initiate treatment as per institutional guidelines. • Consider initiation of corticosteroids equivalent to 1–2 mg/kg/day oral or IV prednisone.

[a] Pembrolizumab may be withheld for a longer period of time (*i.e.*, >12 weeks after event onset) to allow for corticosteroids (if initiated) to be reduced to the equivalent of ≤10 mg/day oral prednisone. The acceptable length of the extended period of time must be based on an assessment of benefit–risk by the investigator and in alignment with the protocol requirements for the duration of treatment and documented by the investigator.

[b] If corticosteroids have been initiated, they must be tapered over ≥1 month to the equivalent of ≤10 mg/day oral prednisone before pembrolizumab can be resumed.

[c] Resumption of pembrolizumab may be considered in patients who are deriving benefit and have fully recovered from the immune-mediated event. The decision to re-challenge patients with pembrolizumab should be based on investigator's assessment of benefit–risk and documented by the investigator (or an appropriate delegate).

Event	Management
Immune-mediated myelitis, Grade 1	• Continue pembrolizumab unless symptoms worsen or do not improve. • Investigate etiology and refer patient to a neurologist.
Immune-mediated myelitis, Grade 2	• Permanently discontinue pembrolizumab. • Investigate etiology and refer patient to a neurologist.

Event	Management
	• Rule out infection. • Initiate treatment with corticosteroids equivalent to 1-2 mg/kg/day oral prednisone.
Immune-mediated myelitis, Grade 3 or 4	• Permanently discontinue pembrolizumab. • Refer patient to a neurologist. • Initiate treatment as per institutional guidelines.

Event	Management
Immune-mediated meningoencephalitis, all grades	• Permanently discontinue pembrolizumab. [a] • Refer patient to neurologist. • Initiate treatment with corticosteroids equivalent to 1–2 mg/kg/day IV methylprednisolone and convert to 1–2 mg/kg/day oral prednisone or equivalent upon improvement. • If event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent. • If event resolves to Grade 1 or better, taper corticosteroids over ≥1 month.

[a] Resumption of pembrolizumab may be considered in patients who are deriving benefit and have fully recovered from the immune-mediated event. The decision to re-challenge patients with pembrolizumab should be based on investigator's assessment of benefit–risk and documented by the investigator (or an appropriate delegate).

9.0 ADVERSE EVENTS

The prompt reporting of adverse events is the responsibility of each investigator engaged in clinical research, as required by Federal Regulations. Adverse events must be described and graded using the terminology and grading categories defined in the NCI's Common Terminology Criteria for Adverse Events (CTCAE), Version 5.0. The CTCAE is available at [redacted] Attribution to protocol treatment for each adverse event must be determined by the investigator and reported on the required forms. Please refer the NCI Guidelines: Adverse Event Reporting Requirements for further details on AE reporting procedures.

9.1 Routine Adverse Event Reporting

Adverse event data collection and reporting, which are required as part of every clinical trial are done to ensure the safety of patients enrolled in the studies as well as those who will enroll in future studies using similar agents. Adverse events are reported in a routine manner at scheduled times according to the study calendar in Section 5.0.

9.1.1 Rave-CTEP-AERS integration

The Cancer Therapy Evaluation Program Adverse Event Reporting System (CTEP-AERS) Integration enables evaluation of post-baseline Adverse Events (AE) entered in Rave to determine whether they require expedited reporting, and facilitates entry in CTEP-AERS for those AEs requiring expedited reporting.

All AEs that occur after baseline are collected in Medidata Rave using the Adverse Event form, which is available for entry at each treatment or reporting period and used to collect AEs that start during the period or persist from the previous reporting period. The CRA

will enter AEs that occur prior to the start of treatment on a baseline form that is not included in the Rave-CTEP-AERS integration. AEs that occur prior to enrollment must begin and end on the baseline Adverse Events form and should not be included on the standard Adverse Events form that is available at treatment unless there has been an increase in grade.

Prior to sending AEs through the rules evaluation process, site staff should verify the following on the Adverse Event form in Rave:

- The reporting period (course/cycle) is correct; and
- AEs are recorded and complete (no missing fields) and the form is query free

The CRA reports AEs in Rave at the time the Investigator learns of the event. If the CRA modifies an AE, it must be re-submitted for rules evaluation.

Upon completion of AE entry in Medidata Rave, the CRA submits the AE for rules evaluation by completing the Expedited Reporting Evaluation form. Both NCI and protocol-specific reporting rules evaluate the AEs submitted for expedited reporting. A report is initiated in CTEP-AERS using information entered in Medidata Rave for AEs that meet reporting requirements. The CRA completes the report by accessing CTEP-AERS via a direct link on the Medidata Rave Expedited Reporting Evaluation form.

In the rare occurrence, that Internet connectivity is lost, a 24-hour notification is to be faxed to the Alliance office at [redacted] Once Internet connectivity is restored, the 24-hour notification that was faxed in must be entered immediately into CTEP-AERS using the deep link from Medidata Rave.

Additional information about the CTEP-AERS integration is available on the CTSU website:

- Study specific documents: Protocols > Documents> Education and Promotion; and
- Expedited Safety Reporting Rules Evaluation user guide: Resources > CTSU Operations Information> User Guides.

NCI requirements for SAE reporting are available on the CTEP website:

- NCI Guidelines for Investigators: Adverse Event Reporting Requirements is available at [redacted]

9.1.2 Solicited adverse events

The following adverse events are considered "expected" and their presence/absence should be solicited, and severity graded, at baseline and for each cycle of treatment.

CTCAE v5.0 Term	**CTCAE v5.0 System Organ Class (SOC)**
Pneumonitis	Respiratory, thoracic and mediastinal disorders
Hyperthyroidism	Endocrine disorders
Colitis	Gastrointestinal disorders

Acute kidney injury	Renal and urinary disorders
Alanine aminotransferase increased	Investigations
Aspartate aminotransferase increased	Investigations
Rash maculo-pupular	Skin and subcutaneous tissue disorders
Papulopustular rash	Infections and infestations
Bullous dermatitis	Skin and subcutaneous tissue disorders

9.2 CTCAE Routine Reporting Requirements

In addition to the solicited adverse events listed in Section 9.1, the following table outlines the combinations of time points, grades and attributions of AEs that require routine reporting to the Alliance Statistics and Data Center. Questions about routine reporting should be directed to the Data Manager.

Combinations of CTCAE Grade & Attribution Required for Routine AE Data Submission on Case Report Forms (CRFs)

Attribution	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Unrelated			a	a	a
Unlikely			a	a	a
Possible		a	a, b	a, b	a, b
Probable		a	a, b	a, b	a, b
Definite		a	a, b	a, b	a, b

a) **Adverse Events: Other CRF** - Applies to AEs occurring between registration and within 30 days of the patient's last treatment date, or as part of the Clinical Follow-Up Phase.

b) **Adverse Events: Late CRF** - Applies to AEs occurring greater than 30 days after the patient's last treatment date.

9.3 Expedited Adverse Event Reporting (CTEP-AERS)

Investigators are required by Federal Regulations to report serious adverse events as defined in the table below. The descriptions and grading scales found in the NCI Common Terminology Criteria for Adverse Events (CTCAE) version 5 will be utilized for AE reporting. The CTCAE is identified and located on the CTEP website at: [redacted] All appropriate treatment areas should have access to a copy of the CTCAE. All reactions determined to be "reportable" in an expedited manner must be reported using the Cancer Therapy Evaluation Program Adverse Event Reporting System (CTEP-AERS).

For further information on the NCI requirements for SAE reporting, please refer to the 'NCI Guidelines for Investigators: Adverse Event Reporting Requirements' document published by the NCI.

Note: All deaths on study require both routine and expedited reporting regardless of causality. Attribution to treatment or other cause should be provided.

9.3.1 Late Phase 2 and Phase 3 Studies: Expedited Reporting Requirements for Adverse Events that Occur on Studies under an IND/IDE within 30 Days of the Last Administration of the Investigational Agent/Intervention[1, 2]

FDA REPORTING REQUIREMENTS FOR SERIOUS ADVERSE EVENTS (21 CFR Part 312)
NOTE: Investigators **MUST** immediately report to the sponsor (NCI) **ANY** Serious Adverse Events, whether or not they are considered related to the investigational agent(s)/intervention (21 CFR 312.64)
An adverse event is considered serious if it results in **ANY** of the following outcomes:

1) Death
2) A life-threatening adverse event
3) An adverse event that results in inpatient hospitalization or prolongation of existing hospitalization for ≥ 24 hours
4) A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
5) A congenital anomaly/birth defect.
6) Important Medical Events (IME) that may not result in death, be life threatening, or require hospitalization may be considered serious when, based upon medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. (FDA, 21 CFR 312.32; ICH E2A and ICH E6).

ALL SERIOUS adverse events that meet the above criteria **MUST** be immediately reported to the NCI via electronic submission within the timeframes detailed in the table below.

<table>
<tr><th>Hospitalization</th><th>Grade 1 Timeframes</th><th>Grade 2 Timeframes</th><th>Grade 3 Timeframes</th><th>Grade 4 & 5 Timeframes</th></tr>
<tr><td>Resulting in Hospitalization ≥ 24 hrs</td><td colspan="2">10 Calendar Days</td><td rowspan="2">24-Hour 5 Calendar Days</td></tr>
<tr><td>Not resulting in Hospitalization ≥ 24 hrs</td><td colspan="2">Not required</td><td>10 Calendar Days</td></tr>
</table>

Expedited AE reporting timelines are defined as:

- "24-Hour; 5 Calendar Days" - The AE must initially be submitted electronically within 24 hours of learning of the AE, followed by a complete expedited report within 5 calendar days of the initial 24-hour report.
- "10 Calendar Days" - A complete expedited report on the AE must be submitted electronically within 10 calendar days of learning of the AE.

[1]Serious adverse events that occur more than 30 days after the last administration of investigational agent/intervention and have an attribution of possible, probable, or definite require reporting as follows:
Expedited 24-hour notification followed by complete report within 5 calendar days for:

- All Grade 4, and Grade 5 AEs

Expedited 10 calendar day reports for:

- Grade 2 adverse events resulting in hospitalization or prolongation of hospitalization
- Grade 3 adverse events

[2]For studies using PET or SPECT IND agents, the AE reporting period is limited to 10 radioactive half-lives, rounded UP to the nearest whole day, after the agent/intervention was last administered. Footnote "1" above applies after this reporting period.

Effective Date: May 5, 2011

9.3.2 Expedited AE reporting timelines defined

- "24 hours; 5 calendar days" – The investigator must initially report the AE via CTEP-AERS ≤ 24 hours of learning of the event followed by a complete CTEP-AERS report ≤ 5 calendar days of the initial 24-hour report.
- "10 calendar days" - A complete CTEP-AERS report on the AE must be submitted ≤ 10 calendar days of the investigator learning of the event.

Any medical event equivalent to CTCAE grade 3, 4, or 5 that precipitates hospitalization (or prolongation of existing hospitalization) must be reported regardless of attribution and designation as expected or unexpected with the exception of any events identified as protocol-specific expedited adverse event reporting exclusions (see below).

Any event that results in persistent or significant disabilities/incapacities, congenital anomalies, or birth defects must be reported via CTEP-AERS if the event occurs following treatment with an agent under an IND.

Use the NCI protocol number and the protocol-specific patient ID provided during trial registration on all reports.

9.3.3 Additional Instructions or Exclusions to CTEP-AERS Expedited Reporting Requirements

All adverse events reported via CTEP-AERS (i.e., serious adverse events) should also be forwarded to your local IRB.

Treatment expected adverse events include those listed in Section 10.0 and in the package insert.

CTEP-AERS reports should be submitted electronically.

Exclusions

Grade 1-3 nausea or vomiting and hospitalization resulting from such do not require AERS reporting, but should be reported via routine AE reporting

Grade 3 nausea or vomiting does not require AERS reporting, but should be reported via routine AE reporting.

Death

Death due to progressive disease should be reported as Grade 5 "Disease progression" in the system organ class (SOC) "General disorders and administration site conditions." Evidence that the death was a manifestation of underlying disease (e.g., radiological changes suggesting tumor growth or progression: clinical deterioration associated with a disease process) should be submitted.

Any death occurring within 30 days of the last dose, regardless of attribution to the investigational agent/intervention requires expedited reporting within 24 hours.

Any death occurring greater than 30 days after the last dose of the investigational agent/intervention requires expedited reporting within 24 hours only if it is possibly, probably, or definitely related to the investigational agent/intervention.

Pregnancy loss and neonatal death

Pregnancy loss is defined in CTCAE as "Death in utero." Any Pregnancy loss should be reported expeditiously, as Grade 4 "Pregnancy loss" under the Pregnancy, puerperium and perinatal conditions SOC. A Pregnancy loss should NOT be reported as a Grade 5 event

under the Pregnancy, puerperium and perinatal conditions SOC, as currently CTEP-AERS recognizes this event as a patient death.

A neonatal death should be reported expeditiously as Grade 4, "Death neonatal" under the General disorders and administration SOC.

New Malignancies

All new malignancies must be reported via CTEP-AERS whether or not they are thought to be related to either previous or current treatment. All new malignancies should be reported, i.e. solid tumors (including non-melanoma skin malignancies), hematologic malignancies, myelodysplastic syndrome/acute myelogenous leukemia, and in situ tumors.

Whenever possible, the CTEP-AERS reports for new malignancies should include tumor pathology, history or prior tumors, prior treatment/current treatment including duration, any associated risk factors or evidence regarding how long the new malignancy may have been present, when and how the new malignancy was detected, molecular characterization or cytogenetics of the original tumor (if available) and of any new tumor, and new malignancy treatment and outcome, if available.

Secondary Malignancy

A secondary malignancy is a cancer caused by treatment for a previous malignancy (e.g., treatment with investigational agent/intervention, radiation or chemotherapy). A secondary malignancy is not considered a metastasis of the initial neoplasm.

CTEP requires all secondary malignancies that occur following treatment with an agent under an NCI IND/IDE be reported via CTEP-AERS. Three options are available to describe the event:

- Leukemia secondary to oncology chemotherapy (e.g., acute myelocytic leukemia [AML])
- Myelodysplastic syndrome (MDS)
- Treatment-related secondary malignancy

Any malignancy possibly related to cancer treatment (including AML/MDS) should also be reported via Rave.

Second Malignancy

A second malignancy is one unrelated to the treatment of a prior malignancy (and is NOT a metastasis from the initial malignancy). Second malignancies require ONLY routine reporting unless otherwise specified.

9.4 Adverse Event Lists for Commercial Agents

Refer to the package inserts for the comprehensive list of adverse events.

Pembrolizumab: Fatigue, musculoskeletal pain, decreased appetite, pruritus, diarrhea, nausea, rash, pyrexia, cough, dyspnea, constipation, pain, and abdominal pain

Nivolumab: Fatigue, rash, musculoskeletal pain, pruritus, diarrhea, nausea, asthenia, cough, dyspnea, constipation, decreased appetite, back pain, arthralgia, upper respiratory tract infection, pyrexia, headache, abdominal pain, and vomiting

Atezolizumab: Fatigue, nausea, cough, dyspnea, and decreased appetite.

Avelumab: Fatigue, fatigue, infusion-related reaction, musculoskeletal pain, nausea, decreased appetite, and urinary tract infection

10.0 DRUG INFORMATION

10.1 General Considerations

All study agents are to be administered at the registering institution.

A list of the adverse events and potential risks associated with the commercial agents administered in this study can be found in Section 9.4.

The total administered dose of chemotherapy may be rounded up or down within a range of 10% of the actual calculated dose.

If the Group credited for enrollment is a non-Alliance Group, then other requirements from the credited Group may apply.

10.2 Pembrolizumab (NSC #7766864, MK-3475)

Formulation

Pembrolizumab injection is a sterile, preservative-free, clear to slightly opalescent, colorless to slightly yellow solution for intravenous use. Each vial contains 100 mg of pembrolizumab in 4 mL of solution. 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.

Storage

Store intact vials between 2°C - 8°C (36°F - 46°F). Do not freeze. Protect from light by storing in the original box.

Stability

Administer prepared solutions immediately after preparation. If not administered immediately, prepared solutions may be stored refrigerated for up to 24 hours. Pembrolizumab solutions may be stored at room temperature for a cumulative time of up to 6 hours. This includes room temperature storage of liquid drug product solution in vials, room temperature storage of infusion solution in the IV bag, and the duration of infusion.

Preparation

Pembrolizumab solution for infusion must be diluted prior to administration. Allow the required number of vials to equilibrate to room temperature. Do not shake the vials. Do not use if opaque or extraneous particulate matter other than translucent to white proteinaceous particles is observed. Do not use if discolored. To prepare the infusion solution add the dose volume of pembrolizumab to an infusion bag containing 0.9% Sodium Chloride Injection, USP or 5% Dextrose Injection, USP. Gently invert the bag 10-15 times to mix the solution. The final concentration must be between **1 mg/mL to 10 mg/mL**.

Compatible IV bag materials: PVC plasticized with DEHP, non-PVC (polyolefin), EVA, or PE lined polyolefin.

Administration

Administer diluted solution by IV over 30 minutes through an intravenous line containing a sterile, non-pyrogenic, low protein binding 0.2 micron to 5 micron in-line or add-on filter. Do not co-administer other drugs through the same infusion line.

Adverse Events

Consult the package insert for the most current and complete information.

10.3 Nivolumab (NSC #748726, BMS-936558, MDX1106)

Formulation

Nivolumab is available in 40 mg/4 mL (10 mg/mL), 100 mg/10 mL (10 mg/mL) and 240 mg/24 mL (10 mg/mL) single dose vials.

Storage

Vials of nivolumab injection must be stored at 2°- 8°C (36°- 46°F) and protected from light and freezing. The unopened vials can be stored at room temperature (up to 25°C, 77°F) and room light for up to 48 hours.

Preparation

Nivolumab injection can be infused undiluted (10 mg/mL) or diluted with 0.9% Sodium Chloride Injection, USP or 5% Dextrose. 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 patients with body weight <40 kg, do not exceed a total volume of infusion of 4 mL/kg of body weight. Mix diluted solution by gentle inversion. Do not shake.

Administration

The administration of undiluted and diluted solutions of nivolumab must be completed within 24 hours of preparation. If not used immediately, the infusion solution may be stored up to 24 hours in a refrigerator at 2°-8°C (36°-46°F) and a maximum of 8 hours of the total 24 hours can be at room temperature (up to 25°C, 77°F) and room light. The maximum 8-hour period under room temperature and room light conditions includes the product administration period.

CAUTION: The single-use dosage form contains no antibacterial preservative or bacteriostatic agent. Therefore, it is advised that the product be discarded 8 hours after initial entry.

Route of Administration: Intravenous infusion over 30 minutes. Do not administer as an IV push or bolus injection.

Method of Administration: Administer through a 0.2 micron to 1.2 micron pore size, low-protein binding in-line filter.

Adverse Events

Consult the package insert for the most current and complete information.

10.4 Atezolizumab (NSC #783608, MPDL3280A)

Formulation

Atezolizumab Injection is available in 840 mg/14 mL (60 mg/mL) and 1200 mg/20 mL (60 mg/mL) single use vials. The solution is colorless to slightly yellow solution.

Storage

2°C-8°C (36°F-46°F) Vial contents should not be frozen or shaken and should be protected from direct sunlight.

Stability

CAUTION: No preservative is used in atezolizumab; therefore, the vial is intended for single use only. Discard any unused portion of drug remaining in a vial.

Preparation

The prescribed dose of atezolizumab should be diluted in 0.9% NaCl and infused through a 0.2 micrometer in-line filter. Dilute to a final concentration between 3.2 mg/mL and 16.8 mg/mL. The IV bag may be constructed of PVC, PO, or PE; the IV infusion line may or may not contain a sterile, non-pyrogenic, low-protein binding in-line filter (pore size of 0.2–0.22 micron).

The prepared solution may be stored either:

- At room temperature for up to 6 hours from the time of preparation. This includes room temperature storage of the infusion in the infusion bag and time for administration of the solution.
- Under refrigeration at 2°C to 8°C (36°F to 46°F) for no more than 24 hours from time of preparation.

Do not freeze or shake the infusion.

Administration

Route of Administration: IV infusion

Method of Administration: Atezolizumab is administered as an intravenous infusion over 60 minutes. If the first infusion is tolerated, all subsequent infusions may be delivered over 30 minutes. Do not administer atezolizumab as an intravenous push or bolus. No premedication is indicated for administration of Cycle 1 of atezolizumab. Patients who experience an infusion related reaction with Cycle 1 of atezolizumab may receive premedication with antihistamines or antipyretics/analgesics (e.g. acetaminophen) for subsequent infusions.

Drug Interactions

Cytochrome P450 enzymes as well as conjugation/glucuronidation reactions are not involved in the metabolism of atezolizumab. No drug interaction studies for atezolizumab have been conducted or are planned. There are no known interactions with other medicinal products or other form of interactions.

Adverse Events

Consult the package insert for the most current and complete information.

10.6 Avelumab (NSC #799232)

Formulation

Avelumab is a clear and colorless to slightly yellow concentrate for solution supplied as a single-dose vial of 200 mg/10 mL (20 mg/mL) and containing D-mannitol, glacial acetic acid, polysorbate 20, sodium hydroxide, and water for injection, and supplied in glass vials closed with a rubber (not made with natural rubber latex) stopper and sealed with an aluminum crimp seal closure fitted with a removable plastic cap.

Storage

Store intact vials at 2-8 ºC (36-46 ºF) in the original container and protected from light. Do not freeze or shake the vial.

Stability

Refer to package labeling for expiration. The diluted drug product should be protected from light and can be stored up to 4 hours at room temperature (up to 25 ºC) or up to 24 hours at 2-8 ºC. If refrigerated, allow the diluted drug product to come to room temperature before administration.

CAUTION: No preservative is used in avelumab; therefore, the vial is intended for single use only. Discard any unused portion of drug remaining in a vial.

Preparation

Avelumab must be diluted prior to administration. Inspect the vials for particulate matter and discoloration. Withdraw the required volume of avelumab from the vial(s) and inject it into a 250 mL infusion bag containing 0.9% sodium chloride injection or 0.45% sodium chloride injection. Gently invert the bag to mix and avoid foaming or excessive shearing. Inspect the solution to ensure it is clear, colorless, and free of visible particles.

Administration

Patients should be pre-medicated with an antihistamine and with acetaminophen prior to the first 4 infusions. Premedication should be administered for subsequent avelumab doses based upon clinical judgement and presence/severity of prior infusion reactions.

Administer the diluted solution as an intravenous infusion over 60 minutes through an intravenous line containing an in-line 0.2-micron low protein binding filter. Do not co-administer other drugs through the same intravenous line.

Adverse Events

Consult the package insert for the most current and complete information.

11.0 MEASUREMENT OF EFFECT

11.1 RECIST 1.1 and iRECIST Criteria

Response and progression will be evaluated in this study using RECIST 1.1 criteria **(25)** and iRECIST criteria **(26)** (See study objectives in Section 2.0). After randomization, disease should be re-evaluated every 12 weeks ± 4 weeks until evidence of progression or relapse (see study calendar in Section 5.0). Imaging assessment will be time-based and not cycle-based.

Baseline scans can include either: 1) a CT, spiral CT, or MRI, or 2) an FDG-PET scan and diagnostic CT. Both IV and oral contrast should be used unless contraindicated, with slide thickness of 5 mm or less. Supporting documentation is to be submitted, per Section 6.1.1. Confirmatory scans should be obtained 4-8 weeks following documentation of objective progression when possible (i.e., clinically stable, without worsening PS or increase in disease-related symptoms). Response assessment should include assessment of all sites of disease, and use the same imaging method as was used at baseline.

Brain imaging and bone scan are required only if there is indication of brain or bone metastases at baseline or if signs or symptoms suggestive of brain or bone metastases develop, respectively. These should follow the same schedule as other cross section imaging (see Sections 5 and 6.3.)

11.1.1 RECIST 1.1 Criteria

Evaluation of Target Lesions

Complete Response (CR): Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to <10 mm (<1 cm).

Partial Response (PR): At least a 30% decrease in the sum of the diameters of target lesions, taking as reference the baseline sum diameters.

Progressive Disease (PD): At least a 20% increase in the sum of the diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also

demonstrate an absolute increase of at least 5 mm (0.5 cm). (Note: the appearance of one or more new lesions is also considered progressions).

Stable Disease (SD): Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum diameters while on study.

Evaluation of Non-Target Lesions

Complete Response (CR): Disappearance of all non-target lesions and normalization of tumor marker level. All lymph nodes must be non-pathological in size (<10 mm [<1 cm] short axis).

Non-CR/Non-PD: Persistence of one or more non-target lesion(s) and/or maintenance of tumor marker level above the normal limits.

Progressive Disease (PD): Appearance of one or more new lesions and/or unequivocal progression of existing non-target lesions. Unequivocal progression should not normally trump target lesion status. It must be representative of overall disease status change, not a single lesion increase.

Although a clear progression of "non-target" lesions only is exceptional, the opinion of the treating physician should prevail in such circumstances, and the progression status should be confirmed at a later time by the review panel (or Principal Investigator).

Evaluation of Best Overall Response

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

For Patients with Measurable Disease (i.e. Target Disease)

Target Lesions	Non-Target Lesions	New Lesions	Overall Response	Best Overall Response when Confirmation is Required*
CR	CR	No	CR	≥4 wks confirmation**
CR	Non-CR/Non-PD	No	PR	≥4 wks confirmation**
CR	Not evaluated	No	PR	
PR	Non-CR/Non-PD/not evaluated	No	PR	
SD	Non-CR/Non-PD/not evaluated	No	SD	Documented at least once ≥4 wks from baseline**
PD	Any	Yes or No	PD	No prior SD, PR or CR
Any	PD***	Yes or No	PD	
Any	Any	Yes	PD	

* See RECIST 1.1 manuscript **(25)** for further details on what is evidence of a new lesion.
** Required only for non-randomized trials with response as primary endpoint. Confirmation of progression is strongly encouraged 4-8 weeks after documentation of PD for this study and should be performed whenever possible (i.e. clinically stable).

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

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

For Patients with Non-Measurable Disease (i.e. Non-Target Disease)

Non-Target Lesions	New Lesions	Overall Response
CR	No	CR
Non-CR/Non-PD	No	Non-CR/Non-PD*
Not all evaluated	No	Not evaluated
Unequivocal PD	Yes or No	PD
Any	Yes	PD

*"Non-CR/Non-PD" is referred over "stable disease" for non-target disease since SD is increasingly used as an endpoint for assessment of efficacy in some trials so to assign this category when no lesions can be measured is not advised.

11.1.2 iRECIST Criteria

The mechanism of action of immune modulating agents, with activation of anti-tumor immune response, has been postulated to lead to unusual patterns of response. Some patients whose disease met criteria for disease progression based on traditional RECIST criteria (i.e. increase in sum of measures of target lesions, unequivocal increase in non-target disease, or appearance of new lesions) were noted to have late responses that are deep and durable. The iRECIST criteria has been developed which allows responses not typically observed in traditional systemic therapies **(26)**. Key comparisons of RECIST 1.1 and iRECIST criteria are summarized below.

	RECIST 1.1	iRECIST
Definitions of measurable and non-measurable disease; numbers and site of target disease	Measurable lesions are 10 mm or more in long diameter (15 mm for nodal lesions); maximum of 5 lesions (2 per organ); all other disease considered not-target (must be 10 mm of longer in short axis for nodal disease)	No change; however, NEW lesions are evaluated as per RECIST 1.1 but are recorded separately on the CRF (but not included in the sum of lesions for target lesions identified at baseline)
CR, PR or SD	Cannot have met criteria for PD prior to CR, PR or SD	May have had iUPD (1 or more instances), but not iCPD, prior to iCR, iPR or iSD
New lesions	Results in PD. Recorded but not measured	Results in iUPD but iCPD is only assigned based on this category if at next assessment • Additional NL appear or • Increase in size of NLs (≥5 mm for sum of NLT or any increase in NLNT)

		NLs, where none have previously been recorded can also confirm iCPD
Consideration of clinical status	Not included in assessment	Clinical stability* is considered in whether treatment is continued after iUPD

Abbreviations: NT = non-target, T = target; NL = new lesions; NLT = new lesion target; NLNT = new lesion non target; iUPD = unconfirmed immune PD; iCPD = confirmed immune PD; SOM= sum of measures. iCR = immune complete response; iPR = immune partial response; iSD = immune stable disease

* Clinical stability requires no worsening in performance status, no clinically relevant increase in disease related symptoms (e.g. pain, dyspnea) felt related to disease progression, and no requirement for intensified management of disease related symptoms including increased analgesia, radiation, or palliative care.

12.0 END OF TREATMENT/INTERVENTION

12.1 Duration of Protocol Treatment

Protocol treatment is to continue until disease progression. Please see the study calendar (Section 5) and the treatment section (Section 7) for treatment and following up time periods.

12.2 Criteria for Discontinuation of Protocol Treatment

Protocol treatment may continue until one of the following criteria applies:

- Disease progression (radiographic by RECIST 1.1 criteria or clinical)
- Intolerable treatment-related adverse event (Arm A only)
- Intercurrent illness that prevents further administration of treatment (Arm A only)
- Unacceptable adverse event(s)
- Patient decides to withdraw from the study
- General or specific changes in the patient's condition render the patient unacceptable for further treatment in the judgment of the investigator (Arm A only)
- Patient non-compliance
- Pregnancy: All women of child bearing potential should be instructed to contact the investigator immediately if they suspect they might be pregnant (e.g., missed or late menstrual period) at any time during study participation. The investigator must immediately notify CTEP in the event of a confirmed pregnancy in a patient participating in the study. The investigator must immediately notify CTEP in the event of a confirmed pregnancy in a patient participating in the study.

The reason(s) for protocol therapy discontinuation, the reason(s) for study removal, and the corresponding dates must be documented in the Case Report Form (CRF).

12.3 Follow-up

12.3.1 Duration of Follow-up

Patients will be followed for survival for 5 years, until death, withdrawal of consent, or the end of the study, whichever occurs first (see Section 5.0).

12.3.2 Follow-up for Patients who Stop Study Treatment Early

- Follow up for patients in Arm A who stop treatment due to reasons other than disease progression (e.g. toxicity)**:** Patients will be followed with physical examination, laboratory, and imaging assessments until radiographic progression, initiation of new treatment, or up to 5 years following registration (See Section 5.0).

- Follow up for patients in Arm A who receive non-protocol therapy: Physical exam, laboratory, and imaging assessments are required within 4 weeks after the end of study treatment. Thereafter, survival information is required every 6 months until 5 years following registration, death, withdrawal of consent, or the end of the study, whichever occurs first **(See Section 5.0)**.

- Follow up for patients in Arm B who receive non-protocol therapy (e.g. restart ICI treatment or new treatment prior to disease progression): Physical exam, laboratory, and imaging assessments are required within 4 weeks before starting non-protocol treatment. Thereafter, survival information is required every 6 months until 5 years following registration, death, withdrawal of consent, or the end of the study, whichever occurs first (See Section 5.0).

12.4 Extraordinary Medical Circumstances

If, at any time the constraints of this protocol are detrimental to the patient's health and/or the patient no longer wishes to continue protocol therapy, protocol therapy shall be discontinued. In this event:

- Document the reason(s) for discontinuation of therapy on data forms.
- Follow the patient for protocol endpoints as required by the Study Calendar.

12.5 Managing ineligible patients and registered patients who never receive protocol intervention

Definition of ineligible patient

A study participant who is registered to the trial but does not meet all of the eligibility criteria is deemed to be ineligible.

Follow-up for ineligible patients who continue with protocol treatment

Patients who are deemed ineligible after registering may continue protocol treatment, provided the treating physician, study chair, and executive officer agree there are no safety concerns if the patient continues protocol treatment. All scans, tests, and data submission are to continue as if the patient were eligible. Notification of the local IRB may be necessary per local IRB policies.

Follow-up for ineligible patients who discontinue protocol treatment

For patients who are deemed ineligible after registering to the trial, who start treatment, but then discontinue study treatment, the same data submission requirements are to be followed as for those patients who are eligible and who discontinue study treatment.

Follow-up for patients who are registered, but who never start study treatment

For all study participants who are registered to the trial but who never receive study intervention (regardless of eligibility), the follow-up requirements are for patients who are eligible and who discontinue study treatment.

13.0 STATISTICAL CONSIDERATIONS

13.1 Study Design

This is a prospective multicenter, randomized, open-label, non-inferiority phase 3 study evaluating the optimal duration of immune checkpoint blockade in patients with locally advanced or metastatic UC. Eligible patients must not have PD per RECIST v1.1 guidelines (i.e., with an ongoing CR, PR or SD) following completion of 12 to 18 months of ICI treatment. Allocation to the two study arms will be performed using stratified randomization as described in Section 4.6. Patients will be randomized 1:1 to continuation of standard of care ICI until disease progression or intolerable toxicity (Arm A) or discontinuation of ICI treatment (Arm B). Patients who progress after treatment discontinuation in Arm B will have the option of restarting the same ICI treatment. This trial implements a non-inferiority design with the primary endpoint of overall survival. Formal interim analysis will be conducted for harm after 25% and 50% of OS events, and the study will be monitored for treatment assignment compliance and feasibility every 6 months.

13.2 Study Endpoints

13.2.1 Primary Endpoint

The primary endpoint is overall survival (OS), which is measured from randomization until death due to any cause. Patients who are lost to follow-up or are not known to be deceased at the time of analysis will be censored at the time of last patient contact.

13.2.2 Secondary Endpoints

Progression-free survival (PFS): This will be assessed using RECIST 1.1 criteria. This will be the time from randomization until disease progression as assessed by RECIST 1.1 or death due to any cause. Patients who are alive and without documented progression will be censored at the time of last disease evaluation.

Immune-related progression-free survival (iPFS): This will be assessed using iRECIST criteria. This will be the time from randomization until disease progression as assessed by irRECIST criteria or death due to any cause. Patients who are alive and without documented progression by iRECIST will be censored at the time of last disease evaluation.

Treatment-free interval (TFI): This is only defined for Arm B (ICI discontinuation) patients and is the time from last dose of ICI to initiation of a subsequent systemic treatment or death. Patients who are alive and have not started a treatment at the time of analysis will be censored at the time of last follow-up.

Rate of response after ICI rechallenge: This is only defined for Arm B (ICI discontinuation) patients. Response after re-initiation of ICI after the first disease progression that occurs after randomization will be assessed using RECIST 1.1.

Adverse events: These will be assessed using CTCAE v5.0.

13.3 Subgroup Analysis

Subgroup analysis may be conducted in the following groups for efficacy endpoints including OS, PFS, and iPFS.

- Response at randomization: CR or PR vs SD
- Type of ICI therapy: Chemotherapy followed by ICI maintenance versus ICI monotherapy first-line versus ICI monotherapy second-line and beyond

- Age: <65 yr vs. ≥65 yr
- Sex: Male vs. Female
- ECOG performance status: 0 or 1 versus 2
- Smoking status: current versus former versus never or unknown
- Histology: transitional cell versus mixed
- Location of primary tumor: upper tract versus lower tract
- Liver metastases (prior to ICI treatment): Yes versus No

13.4 Sample Size Calculation

The sample size was determined with East (v6.4.1) under the following assumptions:

- accrual rate: 15 patients per month
- arm A 24-month OS rate = 50%
- exponential distribution for OS events
- non-inferiority margin, HR = 1.2 (Arm B 24-month OS = 43.5%)
- alpha (one-sided) = 0.05
- power = 80%
- two-interim analysis for harm after 25% and 50% of OS events

This requires a total sample size = 988 evaluable patients (494 in each arm). The sample size will be inflated by 5% to account for patients who withdraw from study prior to starting the protocol, so the target accrual is 1038 patients (or 519 randomized to each arm). In order to accrue the 988 evaluable patients a total of 4500 patients will need to be pre-registered.

13.5 Accrual time and study duration

The anticipated accrual rate is approximately 15 patients per month. Assuming the study proceeds after interim analysis for harm, the maximum expected accrual period is 69 months. Patients will be followed for OS for up to 5 years following registration; therefore, the maximum total study duration (including OS follow-up) is 129 months.

13.6 Primary Analysis Plan

Interim analysis for harm/futility: There will be two interim analyses for overall survival. The first will occur after 25% of deaths (186 deaths) have occurred. This will determine the potential for patient harm. A recommendation will be made to the DSMB to stop the trial for harm if the OS for the discontinuation arm (Arm B) is statistically inferior to the control arm (Arm A) at a one-sided significance level of 0.05. The second interim analysis will be for futility and will occur after 50% of deaths (372 deaths) have occurred. The Wieand rule will be used and the trial will halt for futility if the observed HR is greater than or equal to 1.2 (the non-inferiority margin) **(26).**

Final Analysis: The final analysis will occur after 744 deaths have been observed. It will be an intention-to-treat analysis and will contain all randomized patients with follow-up data. The analysis will test for non-inferiority. If the one-sided 95% CI for the HR contains 1.2, the treatment approach will be declared inferior. The point estimate for the HR and corresponding one-sided 95% CI will be generated with a stratified Cox regression (using the trial stratification factors) that has treatment arm as an exploratory variable.

13.7 Secondary Analysis Plans

A key secondary analysis will be to repeat the primary analysis for the per-protocol population. This will only include eligible patients who were treated according to their randomized assignment. It will exclude patients who withdrew after randomization and prior to receiving protocol treatment.

For the secondary time-to-event endpoints, stratified Cox models will be used to compare the outcomes between the two treatment groups. This includes PFS and iPFS. The subgroup analyses will be done using a stratified Cox model that includes the treatment arm assignment as an explanatory variable and a separate model will be generated for each level for the subgroup of interest.

Tumor responses will be determined for patients on Arm B who had disease progression and re-initiated ICI. The best confirmed tumor response (assessed via RECIST) will be summarized as frequency and relative frequency. The proportion of patients who achieved a tumor response (a CR or PR) will be determined with a binomial point estimate with 95% confidence interval. In addition, an analysis will be done that compares the best confirmed tumor response prior to trial entry to that achieved after ICI re-challenge with a contingency table. A chi-square test (or Fisher's exact test) will be used to determine whether there is an association between the best tumor response prior to trial enrollment and that achieved upon ICI re-challenge.

Adverse events will be summarized with frequencies and relative frequencies. The maximum grade for an AE will be recorded for each patient. The number (percent) of patients that experience each observed adverse event will be summarized. In addition, the proportion of patients that experience a grade 3+, grade 4+, and grade 5 adverse event will be summarized as the number and percent of patients. The primary summary will be regardless of attribution. We will also do an analogous summary for the adverse events that were deemed at least possibly related to treatment.

13.8 Data and Safety Monitoring

The study team and DSMB will monitor the study for compliance and feasibility every 6 months. For the continuation arm (Arm A), if time to treatment discontinuation (censored for discontinuation for unacceptable toxicities) is appreciably faster than PFS (there is a 2 month or greater difference in the estimated of the median time to treatment discontinuation and median PFS), the study may be stopped for lack of compliance. In the discontinuation arm (Arm B), if median treatment free interval (TFI) is less than 6 months, the study may be stopped for lack of feasibility. The proportion of patients who withdraw from study prior to protocol initiation will also be monitored. If after 100 patients are accrued this proportion is 0.15 or greater, the study may be stopped due to unacceptability.

In addition, the DSMB will monitor the trial for safety and whether the trial is meeting its accrual goals in a satisfactory manner.

*For studies assigned **Demography** monitoring **and** enrolling patients via **OPEN**:*

Required submission of patient demographic data for this study will be submitted automatically via OPEN.

Note: Serious adverse events must be submitted via CTEP-AERS per protocol guidelines.

13.9 Inclusion of Women and Minorities

Minorities will be eligible for this study without alteration in eligibility criteria. From prior knowledge, gender or race/ethnicity differences in the intervention effect are not expected. Based on previous data from advanced renal carcinoma patients enrolled on CALGB 90206, the

accrual targets in individual cells are not large enough to perform subgroup analysis by the two treatment groups. This table is based on the accrual profile of urothelial carcinoma patients enrolled to 3 Alliance studies (CALGB 90601 (N-506), A031701 (N=69) and A031501 (N=425)), the Alliance does not anticipate accrual from some subgroups. Therefore, overall accrual to the study will not be extended to meet individual subgroup accrual targets. However, we plan to perform exploratory analyses within gender, racial, and ethnic groups. Both men and women of all races and ethnic groups are eligible for this study.

DOMESTIC PLANNED ENROLLMENT REPORT					
Racial Categories	**Ethnic Categories**				**Total**
	Not Hispanic or Latino		**Hispanic or Latino**		
	Female	**Male**	**Female**	**Male**	
American Indian/ Alaska Native	1	2	2	2	7
Asian	2	12	2	2	18
Native Hawaiian or Other Pacific Islander	2	2	2	2	8
Black or African American	8	19	2	2	31
White	188	648	24	106	966
More Than One Race	2	2	2	2	8
Total	203	685	34	116	1038

- Ethnic Categories:
- Hispanic or Latino – a person of Cuban, Mexican, Puerto Rican, South or Central American, or other Spanish culture or origin, regardless of race. The term "Spanish origin" can also be used in addition to "Hispanic or Latino."
- Not Hispanic or Latino
- Racial Categories
- American Indian or Alaskan Native – a person having origins in any of the original peoples of North, Central, or South America, and who maintains tribal affiliations or community attachment.
- Asian – a person having origins in any of the original peoples of the Far East, Southeast Asia, or the Indian subcontinent including, for example, Cambodia, China, India, Japan, Korea, Malaysia, Pakistan, the Philippine Islands, Thailand, and Vietnam. (Note: Individuals from the Philippine Islands have been recorded as Pacific Islanders in previous data collection strategies.)
- Black or African American – a person having origins in any of the black racial groups of Africa.
- Native Hawaiian or other Pacific Islander – a person having origins in any of the original peoples of Hawaii, Guam, Samoa, or other Pacific Islands.
- White – a person having origins in any of the original peoples of Europe, the Middle East, or North Africa.

14.0 CORRELATIVE AND COMPANION STUDIES

There will be 2 substudies and all patients are encouraged to participate.

14.1 Quality of Life and Health Economics (Alliance A031901-HO1)

14.1.1 Background

The primary objective for this trial is to assess whether discontinuation of ICI (Arm B) versus continued ICI (Arm A) therapy leads to non-inferior overall survival. In terms of quality of life, it is hypothesized that the discontinuation of therapy leads to improved overall quality of life, better quality-adjusted survival, and less fatigue. If indeed this trial demonstrates that the discontinuation of therapy versus continued therapy results in non-inferior overall survival and better quality of life, then these results will directly impact patient care. Therefore, quality of life is an essential component of this trial.

We hypothesize that early discontinuation of ICI in patients will translate into several benefits, including decreased healthcare utilization, improved QOL, less financial toxicity and decreased healthcare costs.

14.1.2 Objectives

Primary Objective

To compare quality-adjusted survival between patients who discontinue ICI therapy vs. receive continuous therapy using EQ-5D-5L. **Hypothesis**: Therapy discontinuation leads to better quality-adjusted survival (defined by combining health utilities at baseline, 6, 12, 18, and 24 months with overall survival) compared to continuous therapy.

Secondary Objectives

- To compare overall QOL as measured by the EORTC QLQ-C30 at each time point between patients who discontinue therapy vs. receive continuous therapy. **Hypothesis**: Therapy discontinuation leads to better quality of life compared to continuous therapy.
- To compare patient-reported fatigue as measured by PROMIS-Fatigue at each time point between patients who discontinue therapy vs. receive continuous therapy. **Hypothesis**: Therapy discontinuation leads to less fatigue compared to continuous therapy.
- To compare healthcare utilization. **Hypothesis**: Therapy discontinuation leads to decreased healthcare utilization.
- To compare incremental cost-effectiveness and cost-utility ratios. **Hypothesis**: Therapy continuation is much more costly but no more effective.
- To compare financial toxicity between patients who discontinue therapy vs. those who received continuous therapy. **Hypothesis**: Therapy discontinuation leads to less financial toxicity.

Exploratory QOL Objective: To compare quality-adjusted survival as measured using EQ-5D-5L versus PROMIS-Preference (PROPr).

14.1.3 Methods

QOL

EQ-5D-5L: This is a 6-item validated utility assessment instrument. The first part consists of 5 items covering 5 dimensions including: mobility, self-care, usual activities,

pain/discomfort, and anxiety/depression. Each dimension can be graded on 5 levels. Health states are defined by the combination of the leveled responses to the 5 dimensions, generating 243 health states to which unconsciousness and death are added. The sixth item is a visual analogue scale for overall health. The 5-item index score is transformed into a health utility score between 0, "Worst health state," and 1, "Best health state." For this study, health utilities (at baseline, 6, 12, 18 and 24 months) for each patient will be combined with overall survival to calculate quality-adjusted survival.

EORTC QLQ-C30: The EORTC QLQ-C30 is one of the most commonly-used QOL instruments in cancer patients, and includes 30 questions broadly applicable to all cancer patients. This instrument is chosen because it has been used in multiple NCTN trials. The instrument assesses 5 functional domains (physical, role, cognitive, emotional, social) and 8 symptoms (fatigue, pain, nausea/vomiting, dyspnea, loss of appetite, insomnia, constipation, diarrhea), together with financial problems and global quality of life.

PROMIS Fatigue: Because fatigue is an important aspect of immunotherapy and there is only a limited assessment of fatigue in EORTC QLQ-C30, PROMIS Fatigue **(27)** is added to study this outcome in more detail. The PROMIS fatigue measures 4 items. An initial item pool of 58 fatigue experience and 54 fatigue impact items were developed. The psychometric properties of these items were evaluated in a sample of 450 individuals from the general US population using classical test theory indices, monotonicity, and scalability. Of note, the 4 questions of PROMIS Fatigue are included in the PROMIS-29 questionnaire (see below).

PROMIS-29+2 v2.1 (PRORr): The PROMIS-29+2 v2.1 includes 29 items from the PROMIS-29 v2.1 plus 2 Cognitive Function Abilities items to enable calculation of a preference score (PROMIS--Preference, PROPr). The preference scores summarize health-related quality of life on a 0 (as bad as dead) to 1 (perfect or ideal health) scale based on PROMIS T-scores for Cognitive Function Abilities, Depression, Fatigue, Pain Interference, Physical Function, Sleep Disturbance, and Ability to Participate in Social Roles and Activities **(28).** The PROMIS-29+2 v2.1 items were selected from PROMIS item banks and calibrated using item response theory. The PROMIS item banks and short forms demonstrate high reliability and validity in the general population and in populations with chronic health conditions **(29)**.

Time points of QOL assessment: All instruments will be assessed at baseline (within 21 days of registration), 6, 12, 18 and 24 months. QOL assessment should continue after disease progression.

Health Economics

Resource Utilization: Resource utilization analysis will take a 2-year horizon. To permit maximum generalizability, data collection will focus on resource utilization rather than costs. Information about treatment delivery, complication management, and post-trial treatments will be captured for all patients through medical record review as part of the clinical trial. Because this study will evaluate the impact of discontinuing immune checkpoint inhibitor therapy among responding patients, knowledge of post-trial therapy is crucial for interpretation of both clinical and economic outcomes. Data will be obtained from the following sources:

Resource utilization	Form
Immunotherapy dose administered, number of cycles	Treatment form (on-study) Completed by CRA

Post-study anti-neoplastic treatments	Post-study treatment form List anti-neoplastic treatments including cytotoxic, biologic and immunotherapy treatments received from the end of study treatment to 24 months or death. List each drug with stop and start date. If a drug is discontinued for >=2 months and then restarted, then indicate STOP on date of last administration and then include a new start. Doses and cycles not required.
Clinic assessments, ER visits, hospitalizations and length of stay, radiation treatment and ICU days	Participant Health Care Resource Utilization Form, completed by the patient at the same time as the QOL forms Data also collected by CRA at 12 and 24 months post-randomization to capture health resource utilization based on medical record review
Survival	Follow-up form Completed by the CRA
Utilities	EQ-5D Completed by the patient at the same time as QOL forms
Financial toxicity	COST-FACIT Completed by the patient at the same time as the QOL forms

Cost estimates will be obtained by applying standard 2020 Medicare reimbursement rates to each item of resource utilization. Economic results will be presented in a disaggregated fashion, i.e., cost = resource utilization x unit cost, where the units of resource use (e.g., number of hospital days) for each resource will be multiplied by the appropriate cost multiplier and summed for each arm of the study. This allows the potential for re-analysis using any cost inputs. Utilities will be captured prospectively on all patients participating in the QOL evaluation with the EQ-5D.

Survival: Survival is the primary endpoint of the clinical trial. Any survival differences found in the trial will be measured as the area between the survival curves for the purposes of the economic evaluation.

Economic analysis will be performed at the completion of the phase 3 portion of the study in accordance with the methodological guidelines set forth by the Second Panel on Cost Effectiveness in Health and Medicine **(30).** If the non-inferiority OS margin is met,

incremental cost-effectiveness and cost-utility ratios will be calculated. If non-inferiority margin is not met, a cost comparison analysis will be conducted. Financial toxicity comparisons will be conducted regardless of the primary OS results.

To capture resource utilization and financial toxicity directly from patients, at each time point that QOL is evaluated, patients will also be asked about major health care episodes that are known cost drivers. Patients will be asked about the number of clinic visits to emergency departments, the number of hospitalizations and the duration of each hospitalization including ICU days. Forms will solicit information about other acute cost drivers including stays in skilled nursing facilities, rehabilitations centers and major operations. Patients will be asked to provide categorical estimates of their direct medical costs for prescription drugs and for transportation. They will also be asked about the financial impact of their medical care using the COST-FACIT questionnaire, a patient-reported outcome measure that describes the financial distress experiences by cancer patients **(31, 32)**.

At 12 months (or at death, whichever is earlier) and 24 months (or death, whichever is earlier), the study data coordinator will complete a medical record review to capture resource utilization for the post-randomization study period.

14.1.4 Statistical Methods

QOL

All questionnaires will be scored according to published scoring algorithms, including recommendations for addressing missing items within a scale. An intent-to-treat approach will be used for all analyses. To evaluate between-arm differences in quality-adjusted survival, each patient's quality-adjusted survival will be calculated using the area under the curve approach (without discounting) based on health utilities derived from the EQ-5D-5Lat baseline, 6, 12, 18 and 24 months. When calculating quality-adjusted survival, the patient's health utility from an earlier assessment will be assumed to be maintained until the patient's next assessment, censoring date, or death (whichever occurs first). Quality-adjusted survival will be compared across arms using a two-sided log-rank test with a nominal significance level of $\alpha = .05$. All data through the follow-up of the earliest censored patient will be used in the quality-adjusted survival analysis. A population-based approach will also be used such that the area under the curve of a quality-adjusted survival curve (i.e., mean health utility multiplied by the proportion of patients surviving based on Kaplan-Meier estimates) is the mean quality-adjusted survival for the population. Mean quality-adjusted survival will be compared between arms using a bootstrap approach **(33).**

As an exploratory analysis, between-arm differences in quality-adjusted survival will be evaluated while calculating each patient's quality-adjusted survival based on health utilities derived from the PROPr (rather than the EQ-5D-5L). The same procedures described above will be used, and results will be compared when deriving patients' health utilities from the EQ-5D-5L versus the PROPr. These comparisons (between the EQ-5D-5L and PROPr) will be used to validate the PROPr and to inform future methodological decisions in the cooperative group setting. To our knowledge, the PROPr has not been implemented and validated in a large phase III trial like A031901.

To evaluate between-arm mean differences in patient-reported quality of life at each time point, a mixed model will be estimated for patient-reported quality of life as assessed by the EORTC QLQ-C30 over the entire study period. The mixed model will include a fixed intercept; fixed effect for time, arm, and arm by time interaction; and residual covariance matrix based on the observed covariances. An unstructured residual covariance matrix will

initially be used, though alternative structures will be investigated with final selection based on convergence of the mixed model and minimization of the Akaike information criterion. The stratification factor used in the randomization as well as baseline patient characteristics and prognostic factors may be included in the mixed model as covariates. Estimates from the mixed model will be used to construct a 95% confidence interval for the mean difference in patient-reported quality of life between arms at each time point. Contrasts estimated via the mixed model will involve a two-sided *t*-test with a nominal significance level of $\alpha = .05$. There will be no adjustment for multiple testing for the secondary QOL objectives.

To evaluate between-arm differences in patient-reported quality of life at each time point, a mixed model will be estimated for patient-reported quality of life as assessed by the EORTC QLQ-C30 over the entire study period. The mixed model will include a fixed intercept; fixed effect for time, arm, and arm by time interaction; and residual covariance matrix based on the observed covariances. An unstructured residual covariance matrix will initially be used, though alternative structures will be investigated with final selection based on convergence of the mixed model and minimization of the Akaike information criterion. The stratification factor used in the randomization as well as baseline patient characteristics and prognostic factors may be included in the mixed model as covariates. Estimates from the mixed model will be used to construct a 95% confidence interval for the mean difference in patient-reported quality of life between arms at each time point. Contrasts estimated via the mixed model will involve a two-sided *t*-test with a nominal significance level of $\alpha = .05$.

The proportion of, and reported reasons for, missing data will be presented by time point and arm. Correlation analysis and logistic regression analysis will be used to examine whether baseline patient characteristics and prognostic factors predict missingness. A sensitivity analysis will be conducted to assess the robustness of the results across various assumptions about the missing data.

Power: To evaluate between-arm differences in quality-adjusted survival, 829 evaluable patients from among the 1,037 randomized patients on the parent protocol (i.e., allowing 10% of patients to decline consent and 10% of patients to miss booklets due to reasons other than death) provide 83% power to detect a difference in quality-adjusted survival between arms based on a two-sided log-rank test, nominal significance level of $\alpha = .05$, and median quality-adjusted survival of 15.6 and 19.2 months in Arms A and B, respectively. Median quality-adjusted survival for Arms A and B were approximated by multiplying median overall survival (i.e., 24 months based on the 24-month overall survival rate of 50%) by health utilities of .65 and .80, respectively (i.e., 24 months × .65 = 15.6 months in Arm A, 24 months × .80 = 19.2 months in Arm B).

To evaluate between-arm differences in patient-reported quality of life at each time point, the number of evaluable patients ranges from 310 to 663 when allowing 10% of patients to decline consent, 10% of patients to miss booklets due to reasons other than death, and 16% (at 6 months) to 50% (at 24 months) of patients to not survive based on a 24-month overall survival rate of 50% in Arms A and B. Power ranges from 62% (at 24 months) to 91% (at 6 months) to detect a mean difference in patient-reported quality of life between arms based on a two-sided *t*-test estimated via a mixed model with 5 assessments per patient, nominal significance level of $\alpha = .05$, intraclass correlation of .50, and population standardized mean difference of 0.20 (i.e., a small effect size based on Cohen's conventions) **(34).** For a population standardized mean difference of 0.35 (i.e., between a small and moderate effect size based on Cohen's conventions) **(34),** power exceeds 95% at all time points (i.e., 6, 12, 18, or 24 months) to detect a mean difference in patient-reported quality of life

between arms. The same power calculations apply when evaluating between-arm differences in patient-reported fatigue at each time point.

Health Economics

Resource utilization analysis will take a 2-year horizon and will evaluate major cost drivers using structured case report forms. Major cost drivers will include the following categories: immunotherapy drug cost, cytotoxic chemotherapy or targeted therapy drug costs, surgical procedures, radiation treatments, ED visits, hospital days, ICU days, outpatient clinic visits, other prescription costs, and transportation costs. Cost data will be derived from both medical record review, much of which overlaps with the review needed to ascertain adverse events, and patient reporting, to capture events occurring at the study site as well as events occurring elsewhere; in the event of discrepancies in cost estimated between medical record and patient reporting, the higher of the two estimates will be used. Unit costs will be assigned based on Medicare reimbursement rates for beneficiaries in fee for service programs for the year 2020. Costs will be standardized to a single year using the medical component of the Consumer Price Index. Economic analysis will be performed at the completion of the phase 3 portion of the study in accordance with the methodological guidelines set forth by the Second Panel on Cost Effectiveness in Health and Medicine **(30).** If the non-inferiority OS margin is met, incremental cost-effectiveness and cost-utility ratios will be calculated. If non-inferiority margin is not met, a cost comparison analysis will be conducted. If cost-utility analyses are calculated they will be performed as follows:

1. Compare the Costs between Arm A and Arm B:

Sum up for Arm A and for Am B: Mean costs of on-study immunotherapy+ mean costs of post-study anti-neoplastic therapy+mean costs of on-study care+mean costs of post-study care + mean on-study prescription drug costs. All estimates will be rounded to the nearest $10. Cost will then be defined as the difference in the sum of mean costs between the two arms ($\$Costs_A$-$\$Costs_B$=$\Delta\$Costs_{A-B}$).

2. Compare Life Years between Arm A and B: The area under the survival curves at 24 months for arm A versus B will be used to estimate the difference in life expectancy. (LY_A-LY_B=ΔLY_{A-B}).

3. Estimate the Quality Adjusted Life Year difference between Arm A and Arm B by multiplying the EQ5D utility weights for Arm A and B respectively by the LYs for each arm.

$QALY_A$-$QALY_B$=$\Delta QALY_{A-B}$

4. Estimate the Incremental Cost-Effectiveness Ratio using the formula:

$\Delta\$Costs_{A-B}$ /ΔLY_{A-B}

5. Estimate the Incremental Cost-Utility Ratio using the formula:

$\Delta\$Costs_{A-B}$ /$\Delta QALY_{A-B}$

Perform Sensitivity Analyses: Estimates of each parameter, including cost, utility, and life year estimates will be varied (+/- 1 standard deviation above and below the mean), and the impact of these changes on the incremental cost-effectiveness ratio and incremental cost-utility ratio will be calculated.

The intervention will be considered cost-effective for at a willingness-to-pay threshold of $100,000 per (quality-adjusted) life-year gained.

6. Compare financial toxicity between Arm A and B (This analysis will be performed regardless of the primary OS results.)

To measure patient-reported financial toxicity, the FACIT-COST will be administered at registration and at 6, 12, 18, and 24 months. It will be scored according to its published scoring algorithm, including recommendations for addressing missing items within the scale. To evaluate between-arm mean differences in patient-reported financial toxicity at each time point, a mixed model will be estimated for patient-reported financial toxicity as assessed by the FACIT-COST over the entire study period. The mixed model will include a fixed intercept; fixed effect for time, arm, and arm by time interaction; and residual covariance matrix based on the observed covariances. An unstructured residual covariance matrix will initially be used, though alternative structures will be investigated with final selection based on convergence of the mixed model and minimization of the Akaike information criterion. The stratification factor used in the randomization as well as baseline patient characteristics and prognostic factors may be included in the mixed model as covariates. Estimates from the mixed model will be used to construct a 95% confidence interval for the mean difference in patient-reported financial toxicity between arms at each time point. Contrasts estimated via the mixed model will involve a two-sided *t*-test with a nominal significance level of $\alpha = .05$.

Power: To evaluate between-arm mean differences in patient-reported financial toxicity at each time point, the number of evaluable patients ranges from 310 to 663 when allowing 10% of patients to decline consent, 10% of patients to miss booklets due to reasons other than death, and 16% (at 6 months) to 50% (at 24 months) of patients to not survive based on a 24-month overall survival rate of 50% in Arms A and B. Power ranges from 62% (at 24 months) to 91% (at 6 months) to detect a mean difference in patient-reported financial toxicity between arms based on a two-sided *t*-test estimated via a mixed model with 5 assessments per patient, nominal significance level of $\alpha = .05$, intraclass correlation of .50, and population standardized mean difference of 0.20 (i.e., a small effect size based on Cohen's conventions) **(34).** For a population standardized mean difference of 0.35 (i.e., between a small and moderate effect size based on Cohen's conventions) **(34)**, power exceeds 95% at all time points (i.e., 6, 12, 18, or 24 months) to detect a mean difference in patient-reported financial toxicity between arms.

14.2 Correlative Science (Alliance A031901-ST1)

The following correlative study outline is provided to justify biospecimen collection. Investigators will submit correlative studies complete protocols including the correlative study objectives, endpoints, sample size, statistical analysis plan including power calculations, etc., once the clinical trial has completed at least 50% accrual and the correlative study appears feasible.

14.2.1 DNA-based biomarkers from tissue

DNA will be extracted from archival tumor specimens for whole exome sequencing (WES). A number of genetic and molecular features in pre-treatment biopsy specimens have been associated with responses to checkpoint inhibitor-based immunotherapy **(35),** including high tumor mutational burden (TMB) and neoantigen load. In addition, high TMB with low burden of copy number loss **(36)** (and particularly intact *PTEN* **(36, 37)** has been associated with response to immunotherapy. The association between these baseline genomic features to clinical outcomes will be evaluated, including attaining CR versus less than CR (e.g., PR or SD) at study entry, time to progression after treatment discontinuation, and recaptured response after treatment rechallenge.

14.2.2 RNA-based biomarkers from tissue

A number of studies have shown that gene expression profiles from tumor tissue are associated with response to immunotherapeutics **(38-41)**. We will perform RNA sequencing from archival tumor specimens and evaluate the association between published gene expression signatures including T-cell inflamed gene expression profile, with clinical outcomes. We will also explore the association between expression of other genes/pathways with clinical outcomes.

14.2.3 PD-L1 immunohistochemistry

In urothelial carcinoma, PD-1/L1 inhibitor monotherapy have demonstrated superior clinical efficacy in PD-L1+ tumors compared to PD-L1- tumors in platinum-refractory mUC patients. While OS benefit with pembrolizumab was observed for both PD-L1 high and PD-L1 low tumors compared to investigators choice of chemotherapy, the degree of benefit was greater in patients with PD-L1 high tumors on subgroup analysis **(8)**. In the first-line setting, interim OS analysis of IMvigor130 demonstrated that in the PD-L1 IC0/1 subgroup, survival favored platinum-containing chemotherapy earlier but atezolizumab later. Conversely, in the PD-L1 IC2/3 subgroup, survival favored atezolizumab. These results indicate that PD-L1 expression is associated with increased benefit from immune checkpoint blockade **(14).** We plan to evaluate the correlation between PD-L1 expression in archival tumor specimens with clinical outcomes, including PFS and OS in both arms. In Arm B, PD-L1 expression will also be associated with duration of response after treatment discontinuation, and response rate after treatment rechallenge.

14.2.4 Characterization of Immune Infiltrate by Immunohistochemistry

The dynamic nature of anti-tumor immune response and intricacy of immune regulation indicate that evaluation of multiple components within the tumor microenvironment is likely to more accurately portray the complete tumor microenvironment and better predict clinical outcomes. We plan to characterize the immune microenvironment through multiplex immunohistochemistry evaluating PD-L1 expression and immune cell subsets, including CD3, CD8 and FoxP3 T cells. Density of pre-treatment CD8+ immune infiltrate (**43)** and CD8+ T cell to CD3+/FoxP3+ regulatory T-cell ratio have been associated with favorable outcomes with immunotherapy **(44),** and we will assess the association of these features with clinical outcomes in our study.

14.2.5 Cell-free methylated DNA and circulating tumor DNA from Blood

Cell-free methylated DNA immunoprecipitation and high-throughput sequencing (cfMeDIP-Seq) is a robust and sensitive methodology for profiling of methylation patterns in cell-free DNA (cfDNA). Recently, cancer (and tissue) specific epigenetic alterations have been identified in a sensitive and accurate manner, including in UC **(45).** This technology provides the opportunity to detect minimal residual disease (MRD) after treatment, as well as early detection of disease progression.

Circulating tumor DNA (ctDNA) can be differentiated from germ-line cell-free DNA through tumor-specific somatic genomic alterations and can be collected non-invasively from a single blood draw. ctDNA has potential to be a biomarker of tumor burden in multiple solid tumor types. The Phase 3 IMvigor011 trial evaluating adjuvant atezolizumab in patients with muscle-invasive bladder cancer failed to meet its primary endpoint; however, prospective ctDNA analysis showed that patients with ctDNA-positive disease had significantly improved clinical outcomes with adjuvant atezolizumab compared to observation **(45)**. Furthermore, a phase 2 study evaluating patients with advanced solid

tumors treated with pembrolizumab showed that baseline ctDNA level as well as changes in ctDNA level with treatment correlates with PFS and OS after immunotherapy **(46)**.

In this study, tumor-specific cfMeDNA and ctDNA will be evaluated as potential indicator of MRD. Detection of cfMeDNA and ctDNA at baseline will be correlated with treatment-free interval after treatment discontinuation, and conversion of undetectable to detectable cfMeDNA to ctDNA, as well as quantification of ctDNA, will be evaluated as an early indicator of disease progression prior to radiographic progression. Tissue-specific cfMeDNA profiles will be evaluated as an early indication of immune-related organ toxicity.

14.2.6 Statistical Considerations

Associations between tumor markers from the primary tumor and clinical outcomes will be evaluated via logistic regression for the tumor response outcome, i.e. attaining CR versus less than CR (e.g., PR or SD). Association between markers and time to event outcomes will be evaluated with Cox proportional hazards models if the outcome is a time-to-event endpoint (e.g. PFS, OS, TFI). When appropriate, the models will include treatment arm as a covariable (e.g. when the analysis is using all patients). The treatment variable will not be used in analyses that uses Arm B patients only (e.g. TFI). The analysis of the association of changes in cfMeDNA and PFS (Arm A and B) and TFI (Arm B only) will only include patients who have a baseline cfMeDNA value and at least one follow-up cfMeDNA value obtained prior to the study visit where a progression event was determined. This analysis will be done using a multivariable Cox model. The model will include the baseline cfMeDNA value as well as a time-dependent variable that indicates the difference in cfMeDNA from baseline at the follow-up visit. For example, if the baseline value was 10 and a follow-up value was 15, the change from baseline variable would be 5. This analysis will be done separately for Arm A and B for PFS, and for Arm B only for TFI and repeated for all patients. The Cox model would contain the treatment arm and would also contain the treatment-arm by cfMeDNA change value interaction term.

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APPENDIX I REGISTRATION FATIGUE/UNISCALE ASSESSMENT

At patient registration, this form is to be administered by a nurse/CRP, completed by the patient, and entered into Medidata Rave at the time of registration.

If needed, this appendix can be adapted to use as a source document. A booklet containing this assessment does not exist – please do not order this booklet.

How would you describe:

your level of fatigue, on the average in the past week including today?

0	1	2	3	4	5	6	7	8	9	10
No Fatigue									Fatigue as bad as it can be	

your overall quality of life in the past week including today?

0	1	2	3	4	5	6	7	8	9	10
As bad as it can be										As good as it can be

APPENDIX II: QOL AND HEALTH ECONOMICS FORMS

Health Questionnaire

English version for the USA

Under each heading, please check the ONE box that best describes your health TODAY.

MOBILITY

I have no problems walking ❑
I have slight problems walking ❑
I have moderate problems walking ❑
I have severe problems walking ❑
I am unable to walk ❑

SELF-CARE

I have no problems washing or dressing myself ❑
I have slight problems washing or dressing myself ❑
I have moderate problems washing or dressing myself ❑
I have severe problems washing or dressing myself ❑
I am unable to wash or dress myself ❑

USUAL ACTIVITIES *(e.g. work, study, housework, family or leisure activities)*

I have no problems doing my usual activities ❑
I have slight problems doing my usual activities ❑
I have moderate problems doing my usual activities ❑
I have severe problems doing my usual activities ❑
I am unable to do my usual activities ❑

PAIN / DISCOMFORT

I have no pain or discomfort ❑
I have slight pain or discomfort ❑
I have moderate pain or discomfort ❑
I have severe pain or discomfort ❑
I have extreme pain or discomfort ❑

ANXIETY / DEPRESSION

I am not anxious or depressed ❑
I am slightly anxious or depressed ❑
I am moderately anxious or depressed ❑

I am severely anxious or depressed	❑
I am extremely anxious or depressed	❑

We would like to know how good or bad your health is TODAY.

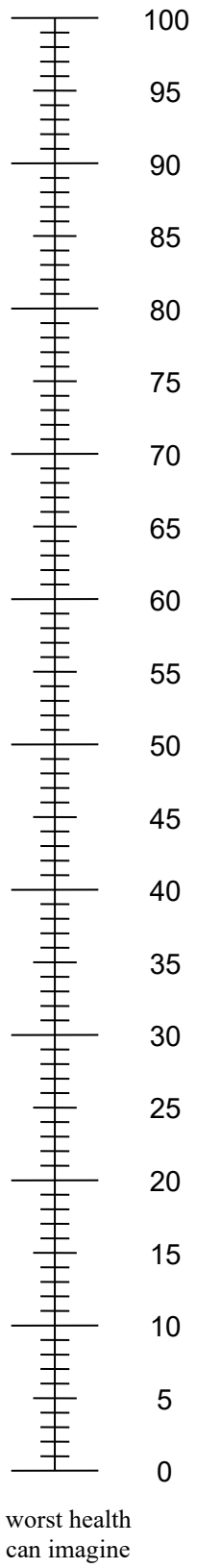
This scale is numbered from 0 to 100.

100 means the best health you can imagine.
0 means the worst health you can imagine.

Mark an X on the scale to indicate how your health is TODAY.

Now, please write the number you marked on the scale in the box below.

YOUR HEALTH TODAY = ☐



PROMIS® 29+2 Profile v2.1 (PROPr)

Please respond to each question or statement by marking one box per row.

	Physical Function	**Without any difficulty**	**With a little difficulty**	**With some difficulty**	**With much difficulty**	**Unable to do**
PFA11	Are you able to do chores such as vacuuming or yard work?	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
PFA21	Are you able to go up and down stairs at a normal pace?	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
PFA23	Are you able to go for a walk of at least 15 minutes?	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
PFA53	Are you able to run errands and shop?	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
	Anxiety **In the past 7 days…**	**Never**	**Rarely**	**Sometimes**	**Often**	**Always**
EDANX01	I felt fearful	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
EDANX40	I found it hard to focus on anything other than my anxiety	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
EDANX41	My worries overwhelmed me	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
EDANX53	I felt uneasy	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
	Depression **In the past 7 days...**	**Never**	**Rarely**	**Sometimes**	**Often**	**Always**
EDDEP04	I felt worthless	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
EDDEP06	I felt helpless	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
EDDEP29	I felt depressed	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
EDDEP41	I felt hopeless	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
	Fatigue **During the past 7 days…**	**Not at all**	**A little bit**	**Somewhat**	**Quite a bit**	**Very much**
HI7	I feel fatigued	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
AN3	I have trouble starting things because I am tired	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

PROMIS® 29+2 Profile v2.1 (PROPr)

	Fatigue **In the past 7 days…**	**Not at all**	**A little bit**	**Somewhat**	**Quite a bit**	**Very much**
FATEXP41	How run-down did you feel on average?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
FATEXP40	How fatigued were you on average?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
	Sleep Disturbance **In the past 7 days…**	**Very poor**	**Poor**	**Fair**	**Good**	**Very good**
Sleep109	My sleep quality was	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
	In the past 7 days…	**Not at all**	**A little bit**	**Somewhat**	**Quite a bit**	**Very much**
Sleep116	My sleep was refreshing.	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
Sleep20	I had a problem with my sleep	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
Sleep44	I had difficulty falling asleep	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
	Ability to Participate in Social Roles and Activities	**Never**	**Rarely**	**Sometimes**	**Usually**	**Always**
SRPPER11_CaPS	I have trouble doing all of my regular leisure activities with others	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
SRPPER18_CaPS	I have trouble doing all of the family activities that I want to do	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
SRPPER23_CaPS	I have trouble doing all of my usual work (include work at home)	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
SRPPER46_CaPS	I have trouble doing all of the activities with friends that I want to do	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
	Pain Interference **In the past 7 days…**	**Not at all**	**A little bit**	**Somewhat**	**Quite a bit**	**Very much**
PAININ9	How much did pain interfere with your day to day activities?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
PAININ22	How much did pain interfere with work around the home?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
PAININ31	How much did pain interfere with your ability to participate in social activities?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

02 January 2020

PROMIS® 29+2 Profile v2.1 (PROPr)

	Pain Interference **In the past 7 days…**	**Not at all**	**A little bit**	**Somewhat**	**Quite a bit**	**Very much**
PAININ34	How much did pain interfere with your household chores?.....	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

	Cognitive Function - Abilities **In the past 7 days…**	**Not at all**	**A little bit**	**Somewhat**	**Quite a bit**	**Very much**
PC6r	I have been able to concentrate	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
PC27r	I have been able to remember to do things, like take medicine or buy something I needed.....	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

	Pain Intensity **In the past 7 days…**											
Global07	How would you rate your pain on average?.....	☐ 0 **No pain**	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6	☐ 7	☐ 8	☐ 9	☐ 10 **Worst pain imaginable**

EORTC QLQ-C30 (version 3)

We are interested in some things about you and your health. Please answer all of the questions yourself by circling the number that best applies to you. There are no "right" or "wrong" answers. The information that you provide will remain strictly confidential.

Please fill in your initials: ☐☐☐☐
Your birthdate (Day, Month, Year): ☐☐☐☐☐☐☐☐
Today's date (Day, Month, Year): 31 ☐☐☐☐☐☐☐☐

	Not at All	A Little	Quite a Bit	Very Much
1. Do you have any trouble doing strenuous activities, like carrying a heavy shopping bag or a suitcase?	1	2	3	4
2. Do you have any trouble taking a long walk?	1	2	3	4
3. Do you have any trouble taking a short walk outside of the house?	1	2	3	4
4. Do you need to stay in bed or a chair during the day?	1	2	3	4
5. Do you need help with eating, dressing, washing yourself or using the toilet?	1	2	3	4

During the past week:

	Not at All	A Little	Quite a Bit	Very Much
6. Were you limited in doing either your work or other daily activities?	1	2	3	4
7. Were you limited in pursuing your hobbies or other leisure time activities?	1	2	3	4
8. Were you short of breath?	1	2	3	4
9. Have you had pain?	1	2	3	4
10. Did you need to rest?	1	2	3	4
11. Have you had trouble sleeping?	1	2	3	4
12. Have you felt weak?	1	2	3	4
13. Have you lacked appetite?	1	2	3	4

14. Have you felt nauseated?	1	2	3	4
15. Have you vomited?	1	2	3	4
16. Have you been constipated?	1	2	3	4
17. Have you had diarrhea?	1	2	3	4
18. Were you tired?	1	2	3	4
19. Did pain interfere with your daily activities?	1	2	3	4
20. Have you had difficulty in concentrating on things, like reading a newspaper or watching television?	1	2	3	4
21. Did you feel tense?	1	2	3	4
22. Did you worry?	1	2	3	4
23. Did you feel irritable?	1	2	3	4
24. Did you feel depressed?	1	2	3	4
25. Have you had difficulty remembering things?	1	2	3	4
26. Has your physical condition or medical treatment interfered with your family life?	1	2	3	4
27. Has your physical condition or medical treatment interfered with your social activities?	1	2	3	4
28. Has your physical condition or medical treatment caused you financial difficulties?	1	2	3	4

For the following questions please circle the number between 1 and 7 that best applies to you

29. How would you rate your overall health during the past week?

1	2	3	4	5	6	7
Very poor						Excellent

30. How would you rate your overall quality of life during the past week?

1	2	3	4	5	6	7
Very poor						Excellent

Healthcare Utilization Form

Dear Study Participant:

We want to understand what resources patients treated on this clinical trial need. We know that some of your care may be at the center where you receive your treatments on this clinical trial. You may also experience the need for treatment elsewhere. Please think back over the past 6 months about health care services that you have needed. Consider services you have received no matter what hospital or clinic you went to**. You do not need exact dates**. **Your best estimates are fine**. You can ask a family member or caregiver to help you complete this form.

Thinking back over the past 6 months, since _____ (date of last assessment) , please complete the following form:

1. Did you require any overnight stays in a hospital?	❑ NO. If NO: Skip to question #3. ❑ YES. If YES: How many days did you spend in the hospital? _____
2. Did you spend any time in the Intensive Care Unit (ICU)?	❑ NO. If NO: Skip to question #3. ❑ YES. If YES: How many days did you spend in the ICU? _____
3. Did you have any operations?	❑ NO. ❑ YES. If YES: Which operation(s)? _____
4. Did you have any visits to an emergency department/acute or urgent care center?	❑ NO. ❑ YES. If YES: How many visits did you make to an emergency department/acute or urgent care center?

	_____
5. Did you spend any days in a rehabilitation or skilled nursing facility?	❑ NO. ❑ YES. If YES: How many days did you spend in a rehabilitation or skilled nursing facility? _____
6. Did you have any outpatient medical procedures include cystoscopy, stents, insertion of tubes or drains, other than any listed under question #3 above?	❑ NO. ❑ YES. If YES: Which procedure(s) did you have? _____
7. Did you have any radiation treatment?	❑ NO. ❑ YES. If YES: How many days of radiation treatment did you have? _____
8. How many outpatient visits did you make to see your cancer doctors (surgeons, medical oncologists, or radiation oncologists) and their practice assistants?	_____
9. How many outpatient visits did you make to see other kinds of doctors (such as primary care physicians, pain or palliative care physicians, or non-cancer related specialists)?	_____
10. About how much did you spend paying out-of-pocket for your outpatient prescription medications?	❑ $0 ❑ < $200 ❑ $200 - $499 ❑ $500 - $999

	❑ $1000 - $5000 ❑ $5000 - $10,000 ❑ > $10,000
11. About how much did you spend paying for transportation to travel back and forth to get your cancer treatments? Include estimates for transportation including gas, parking and any hotel stays you may have needed	❑ $0 ❑ < $200 ❑ $200 - $499 ❑ $500 - $999 ❑ $1000 - $5000 ❑ $5000 - $10,000 ❑ > $10,000

COST-FACIT VERSION 2

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

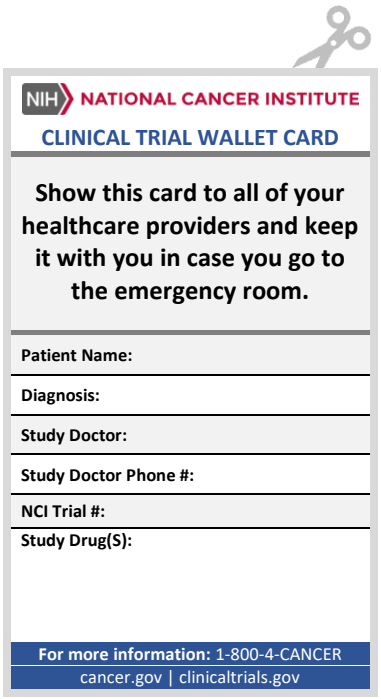
		Not at all	A little bit	Some-what	Quite a bit	Very much
FT1	I know that I have enough money in savings, retirement, or assets to cover the costs of my treatment	0	1	2	3	4
FT2	My out-of-pocket medical expenses are more than I thought they would be	0	1	2	3	4
FT3	I worry about the financial problems I will have in the future as a result of my illness or treatment	0	1	2	3	4
FT4	I feel I have no choice about the amount of money I spend on care	0	1	2	3	4
FT5	I am frustrated that I cannot work or contribute as much as I usually do	0	1	2	3	4
FT6	I am satisfied with my current financial situation	0	1	2	3	4
FT7	I am able to meet my monthly expenses	0	1	2	3	4
FT8	I feel financially stressed	0	1	2	3	4

FT9	I am concerned about keeping my job and income, including work at home	0	1	2	3	4
FT10	My cancer or treatment has reduced my satisfaction with my present financial situation	0	1	2	3	4
FT11	I feel in control of my financial situation	0	1	2	3	4
FT12	My illness has been a financial hardship to my family and me	0	1	2	3	4

English (Universal)

26 September 2017

APPENDIX III: PATIENT CLINICAL TRIAL WALLET CARD



NIH NATIONAL CANCER INSTITUTE

CLINICAL TRIAL WALLET CARD

Show this card to all of your healthcare providers and keep it with you in case you go to the emergency room.

Patient Name:

Diagnosis:

Study Doctor:

Study Doctor Phone #:

NCI Trial #:

Study Drug(S):

For more information: 1-800-4-CANCER

cancer.gov | clinicaltrials.gov