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The world's childhood cancer experts

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A National Cancer Institute-supported member group of the National Clinical Trials Network

December 14, 2021

Martha Kruhm, MS, RAC
Head, Protocol and Information Office
Operations and Informatics Branch
Cancer Therapy Evaluation Program
Division of Cancer Treatment and Diagnosis
National Cancer Institute
Executive Plaza North Room 730
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Dear Ms. Kruhm,

Enclosed please find Amendment #5A to protocol **AREN1721**, *A Randomized Phase 2 Trial of Axitinib/Nivolumab Combination Therapy vs. Single Agent Nivolumab for the Treatment of TFE/Translocation Renal Cell Carcinoma (tRCC) Across All Age Groups*.

This amendment is being done to include proposed language from a stipulation in the PedCIRB's Continuing Review of AREN1721.

Minor administrative updates have been made; specific changes are detailed in the Summary of Changes table below.

Please let me know if you have any questions or need additional information.

Sincerely,

Kathryn Franklin Protocol Coordinator (for)
James Geller, MD, AREN1721 Study Chair,
Jeff Dome, Interim Renal Committee Chair, and
Douglas S. Hawkins, MD, COG Group Chair

AREN1721 SUMMARY OF CHANGES: PROTOCOL

In accordance with the above discussion, the following specific revisions have been made to the protocol. Additions are in **boldfaced** font and deletions in ~~strikethrough~~ font.

#	Section	Page(s)	Change
1.	General	All	Updated protocol version date in the footer.
2.	Cover Page	1	Updated version date and amendment number.
3.	Throughout	Throughout	Updated references to Amendment 5 to Amendment 5**A**

Activated: 10/9/2018
Closed:
Version Date: 12/14/2021
Amendment #: 5A

CHILDREN'S ONCOLOGY GROUP

AREN1721

A Randomized Phase 2 Trial of Axitinib/Nivolumab Combination Therapy vs. Single Agent Nivolumab for the Treatment of TFE/Translocation Renal Cell Carcinoma (tRCC) Across All Age Groups

An Intergroup NCTN Phase 2 Study

Open to Institutions within the United States

NCI Supplied Agents: Axitinib (NSC# 757441, IND#[redacted]), Nivolumab (NSC# 748726, IND#[redacted])
IND sponsor for Axitinib and Nivolumab: DCTD, NCI

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To submit site registration documents:	**For patient enrollments:**	**Submit study data**
Regulatory documentation must be submitted to the CTSU via the Regulatory Submission Portal. Regulatory Submission Portal: (Sign in at www.ctsu.org, and select the Regulatory Submission sub-tab under the Regulatory tab.) Institutions with patients waiting that are unable to use the Portal should alert the CTSU Regulatory Office immediately at 1-866-651-2878 to receive further instruction and support. Contact the CTSU Regulatory Help Desk at 1-866-651-2878 for regulatory assistance.	Please refer to the patient enrollment section of the protocol for instructions on using the Oncology Patient Enrollment Network (OPEN) which can be accessed at https://www.ctsu.org/OPEN_SYSTEM/ or https://OPEN.ctsu.org. Contact the CTSU Help Desk with any OPEN-related questions at ctsucontact@westat.com.	Data collection for this study will be done exclusively through Medidata Rave. Please see the Data Submission Schedule in the CRF packet for further instructions.
The most current version of the **study protocol and all supporting documents** must be downloaded from the protocol-specific Web page of the CTSU Member Web site located at https://www.ctsu.org. 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 user log on with 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 RSS.		
For clinical questions (i.e. patient eligibility or treatment-related) contact the Study PI of the Lead Protocol Organization.		

For non-clinical questions (i.e. unrelated to patient eligibility, treatment, or clinical data submission) contact the CTSU Help Desk by phone or e-mail: CTSU General Information Line – 1-888-823-5923, or ctsucontact@westat.com. All calls and correspondence will be triaged to the appropriate CTSU representative.
The CTSU Website is located at https://www.ctsu.org.

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Agents Supplied by NCI:

AGENT	NSC#
Axitinib (AG-013736)	757441
Nivolumab (MDX-1106)	748726

IND#: [redacted]
IND Sponsor: DCTD, NCI

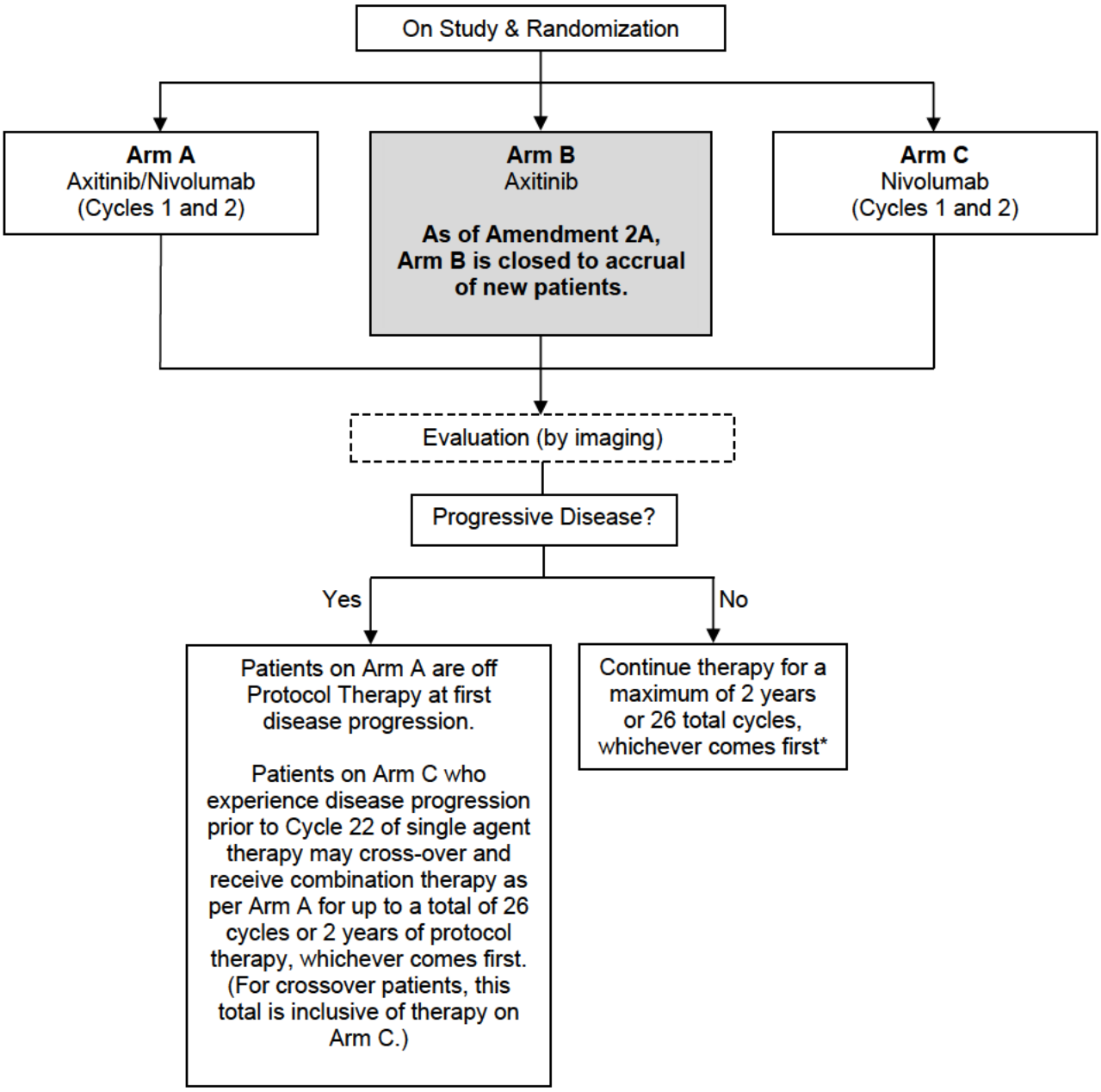
SEE SECTION 15.0 FOR SPECIMEN SHIPPING ADDRESSES

ABSTRACT

TFE/translocation Renal Cell Carcinoma (tRCC) was formally recognized by the WHO in 2004 as a distinct, typically translocation-associated, RCC with characteristic morphology and strong nuclear immunohistochemical expression of transcription factor E3 (TFE3) or transcription factor Eb (TFEb). Cytogenetic translocations may include TFE3-ASPS, TFE3-PRCC, TFEb-alpha, or other variants. TFE3 and TFEb are members of the MiTF/TFE family of basic helix-loop–helix-leucine zipper transcription factors.[1-3] Nearly 50% of pediatric RCCs are tRCC, with a slight female predominance.[4-6] tRCC presents in all races, and accounts for 1-5% of RCC overall, typically in adolescent and young adult ages.[4, 7-11] This will be the first prospective therapeutic study dedicated to tRCC. Efficacy data for VEGFR TKI (axitinib) and PD1/PD-L1 targeted therapy (nivolumab), two key RCC therapeutic targets, will be assessed prospectively as single agents and in combination through a three-way randomization. As of Amendment 2A, Arm B is permanently closed to accrual and the study will proceed as a two-arm randomized trial assessing axitinib and nivolumab in combination or nivolumab alone. As of Amendment 5A, for those patients randomized to the nivolumab arm, cross-over to combination therapy will be permitted at disease progression. All patients treated with axitinib who, at the time, are < 18 years of age, will have pharmacokinetic assessments included.

Important biomarkers of response will be investigated and the biobanking of tissue for this rare cancer will occur. In addition, the behavior of tRCC will be comprehensively described across all ages. Baseline historical data, in combination with efficacy data from anti-angiogenic and immune checkpoint inhibitor therapy, will pave the way for continued future clinical investigation in this patient population.

EXPERIMENTAL DESIGN SCHEMA



1 cycle = 4 weeks.

* Absent disease progression or unacceptable toxicity. Tumor disease status imaging will be assessed after Cycles 2, 4, 6, 9, 12, and then every 4 cycles thereafter, or at any time clinical progression is suspected.

NOTE:

- Patients who have not had cytoreductive nephrectomy prior to trial enrollment but who elect to have cytoreductive nephrectomy during therapy may remain on protocol therapy.
- Cytoreductive nephrectomy is not permitted in the first 12 weeks after starting protocol therapy.
- Axitinib must be held for 7 days before and after surgery. See Section 13.1.2 for more details.

1.0 GOALS AND OBJECTIVES (SCIENTIFIC AIMS)

1.1 Primary Aim

1.1.1 To establish the clinical activity, assessed primarily by progression-free survival, of nivolumab therapy with or without axitinib for advanced transcription factor E3/translocation morphology renal cell carcinoma (TFE/tRCC).

1.2 Secondary Aim

1.2.1 To further define the toxicities of the study arms in the treatment of translocation morphology RCC across all ages.

1.3 Exploratory Aims

1.3.1 To characterize tRCC clinical behavior across all age groups.

1.3.2 To evaluate type of antitumor immune response and stability of T cell activation before and after treatment with immunotherapy or antiangiogenic therapy.

1.3.3 To develop a tumor bank of tRCC tumor samples treated on study for further biological investigations.

1.3.4 To characterize the pharmacokinetics of axitinib when given in combination with nivolumab in pediatric patients with tRCC.

2.0 BACKGROUND

2.1 Introduction/Rationale for Development

Anti-vascular endothelial growth factor (anti-VEGF) receptor tyrosine kinase inhibitors and programmed death-1 (PD-1)/PD-1 ligand (PD-L1) inhibitors (anti-PD1) are either established treatment (anti-VEGF) or are being investigated (anti-PD1) for first-line treatment of patients with metastatic or unresectable renal cell carcinoma (RCC). Neither has been systematically investigated in a variant of RCC called TFE/tRCC.

TFE/tRCC was formally recognized by the WHO in 2004 as a distinct, typically translocation-associated, RCC with characteristic morphology and immunohistochemical expression of TFE3 or TFEb. Cytogenetic translocation partners to TFE3 may include TFE3-ASPS, TFE3-PRCC, TFEb-alpha, or other variants. Mechanisms for TFE upregulation are heterogeneous. TFE3 and TFEb are members of the MiTF/TFE family of basic helix-loop–helix-leucine zipper transcription factors.[1-3] Half of pediatric RCCs are tRCC, with a slight female predominance.[4-6] tRCC occurs in all races, and accounts for 1-5% of RCC, typically in adolescents and young adults.[4, 7-11]

The dominant presentation pattern for tRCC is one of advanced stage and rapid fatality, pointing to an aggressive cancer,[12-15] though infrequent late recurrences[13, 16] and prolonged stable disease[4, 17, 18] point to an infrequently-occurring indolent pattern in a subset of patients. The import of positive lymph nodes, with rates of 41% in younger cohorts[4, 5] and up to 50-80% in older tRCC cohorts,[9, 10] is debated, with reports suggesting both favorable[4, 11, 13, 19] and unfavorable outcomes.[10] Nodal disease is also common with small primary tumors, with rates ranging from 20-33% for T1/T2 disease.[5, 6, 11] Rates of hematogenous metastatic disease range from 9%[5, 11] to 35-75% in select older tRCC cohorts.[10] A meta-

analysis suggests that ASPS-TFE3 RCC is more likely to metastasize than PRCC-TFE3, but only older age or advanced stage, and not fusion subtype, was predictive of death.[13] More recent reports from Korea and China respectively suggest that age > 45 years is an adverse prognostic factor[12], but neither Fuhrman grade nor WHO/ISUP grading is prognostic for tRCC.[20] Overall, in pediatric series, approximately 65% of tRCC cases present with the TNM classification system Stage 3 or 4 disease.[5] For tRCC adult patient cohorts published by medical oncologists, referral patterns may have an impact on stage distribution since low-stage cases are not often referred by urologic oncologists.[9, 10]

Despite typical advance stage at presentation, often aggressive behavior, and apparent increasing awareness and diagnosis of tRCC, no formal treatment recommendations are available, as no dedicated adequately powered prospective therapeutic trials have been conducted. Biological targets of interest include c-Met,[21-23] VEGFR, mTOR,[8, 24, 25] and PD1/PD-L1 immune checkpoint inhibition strategies.[26] Unfortunately, a phase 2 study of the c-MET inhibitor tivantinib did not produce responses in 6 tRCC patients treated, and more recent mTOR inhibitor trials (everolimus; ESPN trial) also failed to demonstrate any benefit in 7 tRCC patients treated.[23, 27]

This will be the first prospective therapeutic study of tRCC to date, combining the resources of the Children's Oncology Group (COG) and other adult cooperative groups through the National Clinical Trials Network (NCTN). Efficacy data for vascular endothelial growth factor receptor (VEGFR) tyrosine kinase inhibitors (TKI) and programmed death-protein 1/programmed death-ligand 1 (PD1/PD-L1) targeted therapy, the two key RCC therapeutic targets, will be assessed prospectively for the first time specifically in tRCC, and the behavior of tRCC comprehensively described across all ages. Inter-group cooperation will be established for study of tRCC along with baseline historical data, and in combination with efficacy data from anti-angiogenic and immune checkpoint inhibitor therapy (as assessed by primary survival endpoints and secondary RECIST-based response metrics), pave the way for continued future clinical investigation in this patient population. Important biomarkers of response will be investigated and a disease-specific tissue bank of this rare cancer will be developed. In sum, this trial will provide the framework for establishing treatment guidelines for tRCC, based on biological and clinical interrogation.

2.1.1 VEGFR TKI in tRCC and Axitinib

VEGFR TKIs are approved by the US FDA for the treatment of clear cell RCC. Evidence of response of tRCCs to VEGFR TKIs is growing, with objective responses and rare durable complete remissions observed in both pediatric and adult patients.[9, 24, 28-33] Malouf et al. reported the results of first-line therapy with sunitinib for tRCC; a median PFS of 8.2 months (n=11) vs. 2 months for cytokines (n=9) was achieved (log-rank p=0.003).[24] Unfortunately, the data from this report, which were extrapolated via retrospective reviews with varying selection criteria, have not been consistently reproduced. Choueiri et al. reported results from a retrospective review of 15 adult tRCC patients treated with anti-VEGF-based therapy (sunitinib [n=10], sorafenib [n=3], monoclonal anti-VEGF antibodies [n=2]) that demonstrated 3 objective responses (20%), 7 stable disease (47%), and 5 progressive disease (33%).[9] Most recently, additional data regarding anti-VEGF based therapy in pediatric patients with tRCC demonstrated a PFS in the 5-8 month range.[34] Second generation more specific and potent VEGFR TKIs are demonstrating promising clinical benefit and diminished off-target effects.

Axitinib is a small molecule inhibitor of VEGFRs 1-3 that was FDA approved in January 2012 for advanced RCC after failure of one prior systemic therapy. Mechanistically, axitinib is a small molecule adenosine triphosphate (ATP)-competitive inhibitor that binds to the unphosphorylated "DFG-out" conformation of the catalytic domain of RTKs. The unique binding mode in the kinase domain affords its selectivity and relative high potency for VEGFRs 1-3 compared with sunitinib, pazopanib, sorafenib, and cedirinib.[35, 36]

2.1.2 PD1/PD-L1 in tRCC and Nivolumab

Recent reports of possibly improved durable response rates using immune checkpoint inhibitor therapy for RCC[26, 37, 38] as compared with historical data using cytokine therapy, coupled with the FDA approval of several such inhibitors for other cancers,[26, 39] have propelled PD1/PD-L1 immune checkpoint inhibitor therapy to the forefront of many RCC-based clinical investigations. The PD-L1 ligand is not expressed in normal kidney but is expressed in many RCC specimens, including 25-30% of tRCC.[26, 40, 41] Specifically, Chang et al reported 25% (9/36) tRCC express PD-L1 which was associated with advanced stage and poor prognosis. Interestingly, PD-L1 tumor expression is associated with a worse clinical outcome in general, and shorter overall survival (OS) in RCC patients treated with anti-VEGF RTKIs.[42]

2.1.3 Closure of Arm B: Axitinib monotherapy arm (Amendment 2A)

As of Amendment 2A, Arm B (the axitinib monotherapy arm) is closed to accrual of new patients. Enrollment challenges related to prohibiting prior anti-VEGF therapy and shifting community practice in favor of emphasizing PD1-targeted therapy in various carcinomas including renal cell carcinoma were key factors that led to the changes in Amendment 2A. Additional information has been recently published regarding the use of combination therapy with axitinib and PD-1/PD-L1 inhibitor compared to sunitinib in adults with advanced RCC.[43, 44]

A key revision in Amendment 2A was to modify the eligibility criteria to permit patients who received one prior anti-VEGF agent to remain eligible for the study. As a result, Arm B (axitinib-only) becomes a less attractive treatment option, particularly for those patients who will have received prior anti-VEGF therapy, contributing to the closure of Arm B. Patients who were enrolled and assigned to Arm B prior to Amendment 2A will continue therapy on Arm B until off protocol therapy criteria is met.

2.2 Adult Studies

2.2.1 Axitinib

Axitinib, an FDA-approved anti-angiogenic therapy for second-line treatment of adult RCC, is the first VEGFR TKI to show superior activity when randomized against another VEGFR TKI (sorafenib) in a pivotal phase 3 RCC trial (AXIS trial), although tRCC was not studied.[35] Importantly, dose titration beyond 5 mg PO BID is feasible in some patients, and appeared to positively impact progression-free survival. Rini et al. recently reported a randomized phase 2 study of axitinib with or without dose titration in first-line metastatic RCC patients, demonstrating a survival advantage to dose titration (42.7 months vs. 30.4 months median survival).[45] In a prior study, Rini et al. reported that optimal axitinib exposure may differ among adult RCC patients, and that PK and blood pressure

could not be used to guide dosing.[46] Nonetheless, criteria for dose titration have included the following criteria for ≥ 2 consecutive weeks: BP ≤ 150/90 mm Hg, no Grade 3/4 axitinib-related toxicities, no prior axitinib dose reductions, and use of no more than 2 concurrent antihypertensive medications.[45]

2.2.2 Nivolumab in RCC

Motzer et al. published results of a phase 2 trial of the PD1 inhibitor nivolumab in metastatic RCC, demonstrating an objective response rate of 20%, 22%, and 20% and median OS of 18.2, 25.5, and 24.7 months for doses of 0.3, 2, and 10 mg/kg given intravenously every 3 weeks, respectively. Responses occurred more commonly in PD-L1 expressing tumors (≥ 5% PD-L1 expression) with overall response rate (ORR) of 31%, but the ORR of 18% for tumors expressing < 5% PD-L1 is still among the best ORRs in RCC. Median OS was not reached in the PD-L1 ≥ 5% group and was 18.2 months in the PD-L1 < 5% group, the latter similar to that achieved with axitinib therapy in the second-line setting.[37] Some responding patients continued to respond for nearly a year after cessation of therapy.[38] Subsequently, results of the CheckMate 025 trial, where patients with advanced RCC previously treated with 1 or 2 regimens of antiangiogenic therapy were randomized to receive either nivolumab 3 mg/kg given q 2 weekly vs. everolimus 10 mg by mouth daily, were reported, demonstrating a median OS of 25 months with nivolumab and 19 months with everolimus. The ORR with nivolumab was 25% (vs. 5% with everolimus). Grade 3 and 4 events were less common with nivolumab (19%) than with everolimus (37%).[39]

2.2.3 Anti-angiogenic plus PD1 Inhibitor Combination Trials

Studies combining anti-angiogenic therapies and PD1 inhibitors in RCC have recently been performed. A trial of nivolumab plus sunitinib confirmed that combining each agent at full dose was tolerable (nivolumab up to 5 mg/kg IV q 3 weekly; sunitinib 50 mg PO daily 4 weeks on/2 weeks off) and demonstrated objective anti-tumor activity (41% ORR by 6 weeks); however, hepatotoxicity was noted. Similarly, combining nivolumab with pazopanib resulted in increased toxicity, notably hepatotoxicity. Specifically, in trial NCT01472081, patients with mRCC (≥ 1 prior systemic therapy) received nivolumab in combination with sunitinib (50 mg, 4 weeks on/2 weeks off; Arm S) or pazopanib (800 mg daily; Arm P), until progression/unacceptable toxicity. The starting dose of nivolumab was 2 mg/kg IV Q3W (N2), with planned escalation to 5 mg/kg IV Q3W (N5). Based on tolerability, the Arm S N5 cohort was expanded to treatment-naïve patients. Primary objectives were safety/tolerability and determination of maximum tolerated dose (MTD) for the combinations; the secondary objective was antitumor activity (ORR and duration of response [DOR]). Seven patients were assigned to each of Arms S N2 and N5. No dose-limiting toxicities (DLTs) were observed and a MTD was not reached, thus N5 was expanded with 19 additional patients (total n=33). Arm P enrolled 20 patients at N2; 4 DLTs (elevated ALT/AST [n=3], fatigue [n=1]) were observed, leading to closure of this arm. Grade 3–4 related AEs were observed in 24/33 patients (73%) in Arm S and 12/20 patients (60%) in Arm P. The most common related Grade 3–4 AEs included elevated ALT (18%), hypertension and hyponatremia (15% each) in Arm S and elevated ALT/AST (20% each) and fatigue (15%) in Arm P. Hepatotoxicities were manageable using treatment algorithms. Grade 3 pneumonitis occurred in 1 patient (Arm S, N5). Grade 3–4 related AEs led to therapy discontinuation in 8/33 patients

(24%; 1 N2, 7 N5) in Arm S and 4/20 patients (20%) in Arm P. ORR was 52% (17/33) in Arm S and 45% (9/20) in Arm P. Responses occurred by first assessment (6 wks) in 41% (Arm S) and 56% (Arm P) of responding patients and were durable (range: Arm S: 12.1+ to 54 wks; Arm P: 12.1 to 69.1+ wks). Stable disease rate was 33% (n=11) in Arm S and 35% (n=7) in Arm P. PFS rate at 24 wks was 78% for Arm S and 55% for Arm P. The authors concluded that nivolumab plus sunitinib or pazopanib showed encouraging antitumor activity and a manageable safety profile in patients with mRCC.[42]

Axitinib has been combined with a PD1 inhibitor (pembrolizumab) in RCC (NCT02133742) and proven tolerable when each agent is administered at its independent MTD/RP2D.[47, 48]

2.3 Pediatric Studies

There have been no combination data for axitinib and nivolumab in children. The Children's Oncology Group has completed accrual to study ADVL1315 (NCT02164838), a phase 1 study of axitinib in pediatric solid tumor patients with relapsed or refractory disease. Oral axitinib tablets were administered BID, continuously in 28-day cycles. Dose Levels 2.4 and 3.2 mg/m^2/dose were evaluated using a rolling 6 design. Serial PK were obtained in Cycle 1. Eighteen patients were enrolled with 1 ineligible (inadequate time from prior therapy). The median age was 13.5 years (range: 5-17 years); 10 were male. Patients received a median 3 prior chemotherapy regimens (range: 1-8). Cancer diagnoses included soft tissue sarcomas (n=7), Ewing (n=3) and osteosarcoma (n=1), neuroblastoma (n=2), Wilms tumor (n=1), hepatoblastoma (n=1), hepatocellular carcinoma (n=1), medullary carcinoma (n=1), and epithelial-myoepithelial carcinoma (n=1). Toxicity data are available for 15 patients (6 patients at Dose Level 1; 5 patients at Dose Level 2, and 4 patients on an expanded PK cohort). Two patients were inevaluable for toxicity due to inadequate drug exposure. DLTs occurred in 0/6 and 2/5 patients treated at Dose Levels 1 and 2, respectively (palmar-plantar erythrodysesthesia syndrome [1]; intratumoral hemorrhage [1]). Cycle 1 hematologic toxicities included Grade 3 lymphopenia (1) and Grade 1 or 2 anemia (4), lymphopenia (3), elevated hemoglobin (3), leukopenia (2), neutropenia (1), thrombocytopenia (1), and lymphocytosis (1). Non-hematologic toxicities included Grade 1 or 2 nausea (5), hypertension (4), anorexia (3), creatinine elevation (2), diarrhea (2), fatigue (2), headache (2), lipase elevation (2), proteinuria (2), and acneiform rash (2). The most common subsequent cycle Grade 3 or 4 toxicities included neutropenia (Grade 3 [3], Grade 4 [1]) and lymphopenia (Grade 3 [1], Grade 4 [1]). Authors concluded that axitinib is tolerated in pediatric patients. The MTD of axitinib given to children with solid tumors is 2.4 mg/m^2/dose, corresponding to 4 mg BID (or 80%) of the adult dose.[49] PK analysis demonstrated peak plasma concentrations 2 h after dose with an average half-life of 0.9 to 5.2 h. There was substantial variability in exposure that appeared to be dose dependent and unexpected accumulation ranging from 0.27- to 4.74-fold. AUC exposures at the pediatric MTD were at levels predicted to be active in adult RCC trials.[49]

In ADVL1315, sixteen patients were evaluable for response; 15 patients had sufficient evaluations to report a response (1 patient did not have all required evaluations obtained). One patient with alveolar soft part sarcoma (also known to be a TFE3 driven cancer) had a confirmed partial response that was durable for 6 months prior to clinical progression of disease and discontinuation of protocol therapy. Five patients had stable disease for up to 6 cycles including 2 patients with osteosarcoma and 1 each with malignant peripheral nerve sheath tumor, Ewing sarcoma, and hepatocellular carcinoma.[49]

COG study ADVL1412 (NCT02304458), *A Phase 1/2 Study of Nivolumab (IND#[redacted]) in Children, Adolescents, and Young Adults with Recurrent or Refractory Solid Tumors as a Single Agent in Combination with Ipilimumab*, is closed to accrual. Full dose therapy analogous to adult trials dosing was confirmed tolerable. (COG ADVL1412 study report)

2.4 Immune Biomarkers

Immunologic evaluations will include PD-L1 expression, type of antitumor immune response and stability of T cell activation before and after treatment. Tissue slides will be used to assess PDL1 expression and TIL composition/distribution before treatment using multicolor imaging. The frequency of tumor infiltrating T cells as well as the expression level of inhibitor molecule PDL-1 on the tumors has been associated with efficacy of PD1 blocking therapy. [50-52]

Peripheral blood mononuclear cells (PBMC) will be assessed for composition of CD4 and CD8 T cells; naïve and memory cells (CD45RO/RA, CCR7), recently activated T cells (HLADR, CD38, Nur77, Ki67), the frequency of T cells with an exhausted phenotype (PD-1, Lag-3, Tim3, CD244), and regulatory phenotype (CD25, FoxP3). It is well established that tumors suppress the immune system and promote the development of immune cells with immune suppressive and tumor promoting capacities including myeloid-derived suppressor cells (MDSC) that directly inhibit cytolytic CD8 T cell proliferation/function and promote angiogenesis and metastases and Tregs that can directly suppress CD8 T cells. In addition, CD8 T cells associated with tumor environments often express a dysfunctional and exhausted phenotype that we aim to overcome with PD1 blocking therapy. Longitudinal assessment of the patients' immune status could provide important clues on the immune mechanisms that may affect immunotherapy efficacy. [53-55]

2.5 Dosing Rationale

2.5.1 Axitinib

2.5.1.1 Adult patients (≥ 18 years of age)

Available data presented above have demonstrated the safety of administering antiangiogenic therapy and PD1 inhibitor therapy in combination to patients with adult RCC at each agent's recommended phase 2 dose (RP2D). In addition, per the axitinib package insert, based on available published data, it has become an accepted standard to dose increase adults with RCC amenable to dose titration upwards beyond 5 mg PO BID. This is an acceptable standard and will be permitted on trial (see Section 4.3.3 and Section 4.4.3).

2.5.1.2 Pediatric patients (< 18 years of age)

Available data (study ADVL1315) noted above has established the RP2D for axitinib as 2.4 mg/m^2/dose (maximum of 5 mg/dose) PO BID.[49] Dose titration will be permitted in patients < 18 years of age on this trial (see Sections 4.3.3, 4.4.3, and Appendix IV).

2.5.2 Nivolumab

2.5.2.1 Adult patients (≥ 18 years of age)

A fixed nivolumab FDA Approved dose of 240 mg IV every 2 weeks or 480 mg IV every 4 weeks will be used for adult patients.

With Amendment #5, adults will have the option to receive nivolumab on one of the above mentioned schedules as both are FDA approved and felt equivalent with regards to efficacy in adult patients.

2.5.2.2 Pediatric patients (< 18 years of age)
The recommended nivolumab dose of 3 mg/kg (up to a maximum dose of 240 mg) IV every 2 weeks will be used for pediatric patients.

2.6 Rationale for Cross-Over Design (Effective with Amendment 5A)

For patients who progress on Arm C (nivolumab monotherapy), evolving clinical options include simple 'continuing beyond progression', change to anti-VEGF TKI-based therapy, or the addition of anti-VEGF TKI-based therapy. The concept of continuing on PD1 inhibitor-based therapy beyond progressive disease, which at times occurs in the setting of mixed responses, has been formally investigated in multiple cancers including renal cell carcinoma.[56-59] Available data suggest that continuing such therapy is both safe, and at times, efficacious,[57, 58] with potential improvements noted in overall survival.[59] That said, either switching to or adding an anti-VEGF TKI-based therapy can be effective in some RCC variants.[60] Considering existing standards in management of RCC and the goals of this trial, cross-over from Arm C (nivolumab monotherapy) to Arm A (combination nivolumab/axitinib therapy) will be permitted for patients on Arm C at first disease progression. Data that results from such cross-over will not impact the primary aim of the study, but will contribute to our understanding of tRCC patient clinical tolerance and response to such therapies, survival outcomes, and pharmacokinetics of axitinib in pediatric patients treated with combination therapy.

2.7 Pharmacokinetics Studies (Effective with Amendment 5A)

COG study ADVL1315 described the phase 1 experience of axitinib in children with relapse/refractory solid tumors, including pharmacokinetic parameters.[49] While helpful, such data remains limited. The FDA has requested that additional PK be obtained in children randomized to Arm A (axitinib/nivolumab) where they are treated with axitinib on study AREN1721 to further characterize the PK specifically in children and adolescents with TFE RCC treated with concurrent nivolumab (a combination for which no PK for axitinib is currently available). AREN1721 also permits the option for axitinib dose escalation beyond doses used in ADVL1315. Such PK data will be used to help define future guidelines of use for axitinib in the pediatric population.

3.0 STUDY ENROLLMENT PROCEDURES AND PATIENT ELIGIBILITY

3.1 Study Enrollment

3.1.1 Patient Registration

Prior to enrollment on this study, patients must be assigned a COG patient ID number. This number is obtained via the Patient Registry module in OPEN once authorization for the release of protected health information (PHI) has been obtained. The COG patient ID number is used to identify the patient in all future interactions with COG. If you have problems with the registration, please refer to the online help. For additional help or information, please contact the CTSU Help Desk at 1-888-823-5923 or ctsucontact@westat.com.

A Biopathology Center (BPC) number will be assigned as part of the registration process. Each patient will be assigned only one BPC number per COG Patient ID.

For additional information about the labeling of specimens please refer to the Pathology and/or Biology Guidelines in this protocol.

Please see Appendix I for detailed CTEP Registration Procedures for Investigators and Associates, and Cancer Trials Support Unit (CTSU) Registration Procedures including: how to download site registration documents; requirements for site registration, submission of regulatory documents and how to check your site's registration status.

NOTE: In order for an institution to maintain COG membership requirements, every patient with a known or suspected neoplasm needs to be offered participation in APEC14B1, *Project:EveryChild A Registry, Eligibility Screening, Biology and Outcome Study.*

3.1.2 IRB Approval

Each investigator or group of investigators at a clinical site must obtain IRB approval for this protocol and submit IRB approval and supporting documentation to the CTSU Regulatory Office before they can be approved to enroll patients. 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 CTSURegPref@ctsu.coccg.org 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 or calling 1-888-651-CTSU (2878).

Sites using their local IRB or REB, must submit their approval to the CTSU Regulatory Office using the Regulatory Submission Portal located in the Regulatory section of the CTSU website. Acceptable documentation of local IRB/REB approval includes:

- Local IRB documentation;
- IRB-signed CTSU IRB Certification Form; and/or
- Protocol of Human Subjects Assurance Identification/IRB Certification/Declaration of Exemption Form.

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.

Additional 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).

For information about the submission of IRB/REB approval documents and other regulatory documents as well as checking the status of study center registration packets, please see Appendix I.

Institutions with patients waiting that are unable to use the Portal should alert the CTSU Regulatory Office immediately at 1-866-651-2878 in order to receive further instruction and support. For general (non-regulatory) questions call the CTSU General Helpdesk at: 1-888-823-5923.

Note: Sites participating on the NCI CIRB initiative and accepting CIRB approval for the study are not required to submit separate IRB approval documentation to the CTSU Regulatory Office for initial, continuing or amendment review.

3.1.3 Reservation Requirements

Prior to obtaining informed consent and enrolling a patient, a reservation must be made following the steps below. Reservations may be obtained 24 hours a day through the Oncology Patient Enrollment Network (OPEN) system. Patients must be enrolled within 5 calendar days of making a reservation.
Note: As of Amendment 5A, each time a reservation is made for a pediatric patient, sites should order a sample collection kit for required pharmacokinetic studies. This is to ensure timely receipt of the kit in the event the pediatric patient is randomized to Arm A, and to ensure a kit is readily available in the event that a patient randomized to Arm C should cross-over to Arm A. See Section 15.1 for complete details.

Patient enrollment for this study will be facilitated using the Slot-Reservation System in conjunction with the registration system in OPEN. Prior to discussing protocol entry with the patient, all site staff must use the CTSU OPEN Slot Reservation System to ensure that a slot on the protocol is available to the patient. Once a slot reservation confirmation is obtained, site staff may then proceed to enroll the patient to this study.

If the study is active, a reservation can be made by following the steps below:

1) Log in to https://open.ctsu.org/open/ using your CTEP IAM user name and password.
2) In order to make a reservation, the patient must have an OPEN patient number. Click on the 'Slot Reservation' tab to create an OPEN patient number, under 'Patients'.
3) Using the OPEN patient number '**RESERVE**' a slot for that patient.
4) On the 'Create Slot Reservation' page, select the Protocol Number, enter the COG Patient ID, and choose the required stratum (if applicable) in order to obtain a reservation.

Refer to the 'Slot Reservation Site User Guide' posted under the 'Help' tab in OPEN for detailed instructions:
https://www.ctsu.org/open/Site_Resources/Training/Users_Manual/CTSU-OPEN-SlotReservationSiteUserGuide.pdf

3.1.4 Study Enrollment

Patient enrollment will be facilitated using the Oncology Patient Enrollment Network (OPEN). 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 Lead Protocol Organization (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 on 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 https://open.ctsu.org or from the OPEN link on the CTSU members' website. Further instructional information is in the OPEN section of the CTSU website at https://www.ctsu.org or https://open.ctsu.org. For any additional questions, contact the CTSU Help Desk at 1-888-823-5923 or ctsucontact@westat.com.

3.1.5 Timing

Patients must be enrolled before treatment begins. The date protocol therapy is projected to start must be no later than **five (5)** calendar days after the date of study enrollment. **Patients who are started on protocol therapy on a phase 2 study prior to study enrollment will be considered ineligible**.

All clinical and laboratory studies to determine eligibility must be performed within 7 days prior to enrollment unless otherwise indicated in the eligibility section below.

3.2 Patient Eligibility Criteria

Important note: The eligibility criteria listed below are interpreted literally and cannot be waived. All clinical and laboratory data required for determining eligibility of a patient enrolled on this trial must be available in the patient's medical/research record which will serve as the source document for verification at the time of audit.

All clinical and laboratory studies to determine eligibility must be performed within 7 days prior to enrollment unless otherwise indicated. Laboratory values used to assess eligibility must be no older than seven (7) days at the start of therapy. Laboratory tests need not be repeated if therapy starts within seven (7) days of obtaining labs to assess eligibility. If a post-enrollment lab value is outside the limits of eligibility, or laboratory values are > 7 days old, then the following laboratory evaluations must be re-checked within 48 hours prior to initiating therapy: CBC with differential, bilirubin, ALT (SGPT), and serum creatinine. If the recheck is outside the limits of eligibility, the patient may not receive protocol therapy and will be considered off protocol therapy.

Imaging studies, if applicable, must be obtained within 4 weeks prior to enrollment and start of protocol therapy (repeat the tumor imaging if necessary).

Echocardiogram, must be obtained within 8 weeks prior to enrollment and start of protocol therapy (repeat echocardiogram if necessary).

3.2.1 Age
Patients must be ≥ 12 months at enrollment.

3.2.2 Body Surface Area (BSA)
Patients must have a Body Surface Area (BSA) ≥ 0.53 m^2.

3.2.3 Diagnosis
Histologically confirmed unresectable or metastatic translocation morphology renal cell carcinoma diagnosed using WHO-defined criteria. Patients may be newly diagnosed or have received prior cancer therapy.

3.2.3.1 Patients must have had histologic verification of the malignancy.

3.2.3.2 Patients must have measurable disease, documented by clinical, radiographic, or histologic criteria as defined by RECIST v1.1.

3.2.3.3 Patients must have a tumor showing the appropriate morphologic appearance, and either confirmed TFE3 nuclear protein expression by immunohistochemistry with appropriate positive and negative controls performed at a CLIA-certified laboratory, or evidence of TFE3 or TFEb translocation by either FISH or RT-PCR performed at a CLIA-certified laboratory. For TFE3 immunohistochemistry, any nuclear positivity in the presence of appropriate positive and negative controls should be considered as evidence of TFE3 immunohistochemical expression.
NOTE: If the institution is unable to perform these studies, unstained slides may be submitted to Dr. Elizabeth Perlman, who will perform TFE3 analysis at no charge. The slide will be returned to the referring institution for local evaluation, to be included in their institutional report. See Section 14.1.2 for complete details.

3.2.4 Performance Level
Patients must have a performance status corresponding to ECOG scores of 0, 1 or 2. Use Karnofsky for patients > 16 years of age and Lansky for patients ≤ 16 years of age. See Appendix II.

3.2.5 Life Expectancy
Patients must have a life expectancy of ≥ 8 weeks.

3.2.6 Prior Therapy
Patients must have fully recovered from the acute toxic effects of all prior chemotherapy, immunotherapy, or radiotherapy prior to entering this study.

a. Myelosuppressive chemotherapy: Must not have received within 2 weeks of entry onto this study (6 weeks if prior nitrosourea).
b. Immunotherapy: Must not have received within 4 weeks of entry onto this study.
c. Biologic (anti-neoplastic agent): At least 7 days since the completion of therapy with a biologic agent.
d. Radiation therapy (RT): ≥ 2 weeks for local palliative RT (small port); ≥ 6 months must have elapsed if prior craniospinal RT or if ≥ 50%

radiation of pelvis; ≥ 6 weeks must have elapsed if other substantial BM radiation.

3.2.7 Organ Function Requirements

3.2.7.1 Adequate Bone Marrow Function Defined As:

- Peripheral absolute neutrophil count (ANC) ≥ 1000/μL
- Platelet count ≥ 75,000/μL (transfusion independent)
- Hemoglobin ≥ 8.0 g/dL (may receive RBC transfusions)

3.2.7.2 Adequate Renal Function Defined As:

- Urine protein: ≤ 30 mg/dL in urinalysis or ≤ 1+ on dipstick, unless quantitative protein is < 1000 mg in a 24 h urine sample.
- **For patients < 18 years of age:** Serum creatinine ≤ 1.5 X upper limit of normal (ULN), or measured or calculated* creatinine clearance or radioisotope GFR ≥ 60 mL/min/1.73 m^2 for patient with creatinine levels > 1.5 X institutional ULN, or a serum creatinine based on age/gender as follows:

Age	Maximum Serum Creatinine (mg/dL)	
	Male	Female
1 to < 2 years	0.6	0.6
2 to < 6 years	0.8	0.8
6 to < 10 years	1	1
10 to < 13 years	1.2	1.2
13 to < 16 years	1.5	1.4
≥ 16 years	1.7	1.4

The threshold creatinine values in this table were derived from the Schwartz formula for estimating GFR utilizing child length and stature data published by the CDC.[61]

- **For patients ≥ 18 years of age:** Serum creatinine ≤ 2 X ULN, or measured or calculated* creatinine clearance or radioisotope GFR ≥ 40 mL/min/1.73 m^2 for patient with creatinine levels > 2 X institutional ULN.

*Creatinine clearance should be calculated per institutional standard.

3.2.7.3 Adequate Liver Function Defined As:

- Serum total bilirubin ≤ 1.5 X ULN for age, or direct bilirubin ≤ ULN for patients with total bilirubin levels > 1.5 X ULN.
- SGOT (AST) or SGPT (ALT) < 3 X ULN for age.
- Albumin > 2.5 mg/dL.

3.2.7.4 Adequate Cardiac Function Defined As:

- Shortening fraction of ≥ 27% by echocardiogram, or
- Ejection fraction of ≥ 50% by radionuclide angiogram.
- No history of myocardial infarction, severe or unstable angina, or peripheral vascular disease.
- QTc ≤ 480 msec. Note: Patients with Grade 1 prolonged QTc (450-480 msec) at the time of study enrollment should have

correctable causes of prolonged QTc addressed if possible (i.e., electrolytes, medications).

3.2.7.5 Adequate Coagulation Function Defined As:

- International Normalized Ratio (INR) or Prothrombin Time (PT) ≤ 1.5 X ULN. However, if patient is receiving anticoagulant therapy, PT or PTT should be within therapeutic range of intended use of anticoagulants.
- Activated Partial Thromboplastin Time (aPTT) ≤ 1.5 X ULN unless patient is receiving anticoagulant therapy as long as PT or PTT is within therapeutic range of intended use of anticoagulants.

3.2.7.6 Adequate Blood Pressure Control Defined As:

- A baseline blood pressure (BP) ≤ the 95th percentile for age, height, and gender for patients < 18 years old (see Appendix III), or ≤ 150 mmHg (systolic) and ≤ 90 mmHg (diastolic) for patients ≥ 18 years old.
  Note: 2 serial blood pressures should be taken at least 1 hour apart and averaged to determine baseline BP (see Section 5.2.5.1).
- Patients are eligible if on stable doses (≥ 7 days) of anti-hypertensive medications with a baseline BP meeting the criteria above.

3.2.8 Exclusion Criteria

3.2.8.1 Patients unable to swallow whole tablets.

3.2.8.2 Patients who in the opinion of the investigator are not able to comply with the study procedures are not eligible.

3.2.8.3 Prior Therapy

- Patients who have received prior therapy with axitinib, nivolumab, or other PD1/PD-L1 targeted therapies.
- Patients who have received prior therapy with more than one anti-VEGF based agent (antibody or tyrosine kinase inhibitor).
- Patients with hypersensitivity to axitinib, nivolumab, or any of its excipients.
- Patients who previously received an allogeneic stem cell transplant (SCT) or solid organ transplant are not eligible.
- Patients may not be receiving any other investigational agents (within 4 weeks prior to study enrollment).
- Patients who have received prior anti-cancer monoclonal antibody (mAb) within 4 weeks prior to study enrollment or who have not recovered (i.e., ≤ Grade 1 or at baseline) from adverse events due to agents administered more than 4 weeks prior to enrollment.
- Surgery: Patients who have had or who are planning to have the following invasive procedures are not eligible:
  - Major surgical procedure, laparoscopic procedure, open biopsy, core biopsy, fine needle aspirate, or significant traumatic injury within 7 days prior to enrollment. **NOTE:** External central lines must be placed at least 3 days prior to

planned treatment initiation and subcutaneous ports must be placed at least 7 days prior to planned treatment initiation.
    - Patients who are planning cytoreductive surgery within the first 12 weeks following therapy initiation.
    - Patients who have a serious or non-healing wound or ulcer at the time of study enrollment are not eligible.
- Patients who have a history of abdominal fistula, gastrointestinal perforation, or intra-abdominal abscess within 28 days of study enrollment are not eligible.
- Patients who have received prior targeted small molecule therapy within 2 weeks of enrollment or have not recovered (i.e., ≤ Grade 1 or at baseline) from adverse events due to agents administered more than 4 weeks prior to enrollment. **NOTE:** Subjects with ≤ Grade 2 neuropathy are an exception to this criterion and may qualify for the study.

3.2.8.4 Pre-existing conditions, which may include:

- Additional known malignancy that is progressing or requires active treatment. Exceptions include basal cell carcinoma of the skin, or squamous cell carcinoma of the skin that has undergone potentially curative therapy, or in situ cervical cancer.
- Patients with underlying immune deficiency, chronic infections including hepatitis, tuberculosis (TB), or autoimmune disease.
- HIV-infected patients with the exception of patients on an effective anti-retroviral therapy with an undetectable viral load within 6 months prior to enrollment.
- Patients with underlying hematologic issues including congenital bleeding diathesis, known previous GI bleeding requiring intervention within the past 6 months, history of hemoptysis within 42 days prior to study enrollment, active pulmonary emboli, or deep vein thromboses (DVT) that are not stable on anticoagulation regimen.
- Patients must not have had significant vascular disease (i.e. Moya-Moya, aortic aneurysm requiring surgical repair).
- A known history of, or any evidence of active, non-infectious pneumonitis.
- Patients with known active central nervous system (CNS) metastases and/or carcinomatous meningitis or leptomeningeal disease. Patients with previously treated brain metastases may participate provided they are stable (without evidence of progression by imaging for at least 4 weeks prior to study enrollment and any neurologic symptoms have returned to baseline), have no evidence of new or enlarging brain metastases, and are not using steroids for at least 7 days prior to study enrollment. This exception does not include carcinomatous meningitis which is excluded regardless of clinical stability.
- Any uncontrolled, intercurrent illness including but not limited to ongoing or active infection, symptomatic congestive heart failure, unstable angina pectoris, cardiac arrhythmia.

- Any serious medical or psychiatric illness/condition including substance use disorders likely in the judgment of the Investigator(s) to interfere or limit compliance with study requirements/treatment.
- Patients with active autoimmune disease that has required systemic treatment in the past 2 years (i.e. with use of disease modifying agents, corticosteroids or immunosuppressive drugs). Replacement therapy (e.g., thyroxine, insulin, or physiologic corticosteroid replacement therapy for adrenal or pituitary insufficiency, etc.) is not considered a form of systemic treatment.

3.2.8.5 Treatments and/or medications the patient is receiving or has received that would make her/him ineligible, including:

- Concomitant (or receipt of) treatment with medications that may affect the metabolism of nivolumab and/or axitinib within 7 days prior to planned first dose of protocol therapy.
- A live vaccine within 30 days of planned first dose of protocol therapy. **NOTE:** Inactivated flu vaccines are allowed; however intranasal influenza vaccines (e.g., Flu-Mist®) are live attenuated vaccines, and are not allowed.

3.2.8.6 Pregnancy and Breast Feeding

3.2.8.6.1 Due to risks of fetal and teratogenic adverse events as seen in animal studies, a negative pregnancy test must be obtained in females of childbearing potential, defined as females who are post-menarchal. If the urine test is positive or cannot be confirmed as negative, a serum pregnancy test will be required.

3.2.8.6.2 Females of childbearing potential that are sexually active must agree to either practice 2 medically accepted highly-effective methods of contraception at the same time or abstain from heterosexual intercourse from the time of signing the informed consent through 5 months after the last dose of study drug.

3.2.8.6.3 Lactating females are not eligible unless they have agreed not to breastfeed their infants starting with the first dose of study therapy through 5 months after the last dose of study therapy.

3.2.8.7 Male patients of reproductive potential must agree to use an adequate method of contraception starting with the first dose of study therapy through 7 months after the last dose of study therapy. Prior history of vasectomy does <u>not</u> replace requirement for contraceptive use.

3.2.9 <u>Regulatory Requirements</u>

3.2.9.1 All patients and/or their parents or legal guardians must sign a written informed consent.

3.2.9.2 All institutional, FDA, and NCI requirements for human studies must be met.

4.0 TREATMENT PROGRAM

Timing of protocol therapy administration, response assessment studies, and surgical interventions are based on schedules derived from the experimental design or on established standards of care. Minor unavoidable departures (up to 72 hours) from protocol directed therapy and/or disease evaluations (and up to 1 week for surgery) for valid clinical, patient and family logistical, or facility, procedure and/or anesthesia scheduling issues are acceptable (except where explicitly prohibited within the protocol).

4.1 Overview of Treatment Plan

Prior to Amendment 2A, the study was a randomized three-arm phase 2 study evaluating the clinical benefit of axitinib, nivolumab, and their use in combination for the treatment of tRCC.

As of Amendment 2A, Arm B (axitinib alone) is permanently closed to accrual, and prospective patients will be randomly assigned to one of the following arms:
Arm A: Axitinib + Nivolumab
Arm C: Nivolumab

As of Amendment 5A, patients who are initially randomized to Arm C (nivolumab alone) and experience progressive disease prior to Cycle 22 will be permitted to crossover to Arm A (axitinib + nivolumab). For patients who crossover to Arm A, they are to continue on their current nivolumab schedule and start axitinib as soon as it is made available. NOTE: Patients must use the NCI supplied drug. Commercially supplied axitinib is not allowed.

Axitinib will be administered at a starting dose of 5 mg PO BID for patients ≥ 18 years of age, and at 2.4 mg/m^2/dose (maximum of 5 mg/dose) PO BID for patients < 18 years of age. See Appendix IV for axitinib dosing nomogram. Individual patient dose titration of axitinib (escalation from starting dose) is permitted on protocol therapy, at the discretion of the treating physician. Refer to Section 4.3.3 or 4.4.3 for dose titration criteria.

Nivolumab will be given at either 240 mg IV every 2 weeks or 480 mg IV every 4 weeks for patients ≥ 18 years of age, and at 3 mg/kg IV (maximum of 240 mg/dose) every 2 weeks for patients < 18 years of age. Pre-medication is not required as infusion reactions are rare, but anaphylactic precautions should be observed during each infusion of nivolumab. If ≥ Grade 2 infusion reaction occurs, the infusion should be stopped and supportive care given as per institutional guidelines. See Section 5.3 for management and dose modification guidelines for infusion reactions. Investigators are advised to monitor for fever, chills, shakes, itching, rash, hypertension or hypotension, or difficulty breathing during and immediately after administration of nivolumab.

Combination therapy will be given with agents at full single agent doses as above.

Each cycle of therapy will be 4 weeks. Tumor disease evaluation will occur after Cycles 2, 4, 6, 9, 12, and then every 4 cycles thereafter, or at any time clinical progression is suspected. If pseudoprogression is suspected (until any degree of response is observed), disease evaluation must occur after every cycle (Section 10.2.1). Absent disease

progression or unacceptable toxicity, patients may continue on protocol therapy for up to 2 years duration or completion of 26 cycles, whichever comes first. Disease evaluations (including imaging) will continue during follow-up according to the schedule outlined in Section 7.2.

For patients who progress on Arm C prior to Cycle 22, cross-over to Arm A is permitted. Patients should resume Arm A therapy as soon as PD is identified. Nivolumab should continue uninterrupted according to the previously established schedule for that patient (either every 2 or 4 weeks). Axitinib should be added as soon as it becomes available from NCI and the patient has recovered from any relevant toxicity. Subsequent disease evaluations should occur as above timed from the first cycle of combination therapy The first cycle of combination therapy after cross-over will be defined as the cycle for which > 14 days of axitinib is given, with Day 1 of Cycle 1 after cross-over defined as the day of first nivolumab dose during that cycle after axitinib is started or on the day axitinib is started if given concurrently. **NOTE:** The total protocol therapy received on AREN1721 (whether delivered on Arm A, Arm C, or Arm C+A) is not to exceed 26 cycles or 2 years, whichever comes first.

NOTE:

- Patients who have not had cytoreductive nephrectomy prior to trial enrollment but who elect to have cytoreductive nephrectomy during therapy may remain on protocol therapy.
- Cytoreductive therapy is not permitted in the first 12 weeks after starting protocol therapy.
- Axitinib must be held for 7 days before and after surgery. See Section 13.1.2 for more details.

For COG Supportive Care Guidelines see:
https://childrensoncologygroup.org/index.php/cog-supportive-care-guidelines.

4.2 Concomitant Therapy

4.2.1 Patients may not receive other anti-cancer medications while on protocol therapy.

4.2.2 Small port radiotherapy and/or surgery for management of persistent and/or symptomatic tumor is permitted while on protocol therapy.

4.2.3 Patients may not have surgical resection of the tumor during the first 12 weeks of protocol therapy per Section 13.1.8.1.

4.2.4 Patients who have surgical resection of lesions that are increasing in size while on therapy must be removed from protocol therapy per Section 13.1.8.2.

4.2.5 If not done prior to study enrollment, cytoreductive nephrectomy should be reconsidered after 12 weeks of protocol therapy, taking into account the need to hold axitinib before and after surgery per Section 13.1.8.3.

4.2.6 Supportive care per institutional guidelines is permitted.

4.2.7 Steroid therapy is permitted as clinically indicated, though it is recommended that use of steroids in patients on nivolumab be limited to use for management of

immune-related adverse events per standard guidelines (see Section 5.3 for Dose Modifications).

4.2.8 Anti-hypertensives

Patients who develop hypertension while on protocol therapy may be treated with anti-hypertensive agents and may remain on protocol therapy as long as hypertension is well controlled on medication. The algorithms in Section 5.2.5 will be used to grade and manage axitinib-related hypertension.

4.2.9 CYP3A4 Inhibitors and Inducers

Axitinib is a major substrate for cytochrome P-450 3A4 isozyme. Strong inducers or inhibitors of CYP3A4 may alter the pharmacokinetics of axitinib and should be avoided for 7 days prior to enrollment. They should also be avoided for the duration of protocol therapy for patients in Arms A and B. Moderate inducers or inhibitors of CYP3A4 should be avoided as well, if reasonable alternatives exist. Please see Appendix VI for list of CYP3A4 inducers and inhibitors. Because the lists of these agents are constantly changing, it is important to regularly consult frequently updated medical references.

4.3 Arm A: Axitinib + Nivolumab

4.3.1 Therapy Delivery Map – Arm A: Axitinib + Nivolumab

Each cycle lasts 28 days (4 weeks). Absent disease progression or unacceptable toxicity, patients may continue on protocol therapy for up to 2 years duration or completion of 26 cycles, whichever comes first.
This TDM is on 3 pages. A copy of this TDM will be used for each cycle; please enter the cycle # below.

Patient COG ID number

DOB

Criteria to start each cycle: ANC ≥ 1000/µL, platelet count ≥ 75,000/µL without transfusion support. See Section 5.0 for other requirements related to any ongoing toxicities.

DRUG	ROUTE	DOSAGE		DAYS	IMPORTANT NOTES
Axitinib (IND#[redacted]) **Do not use commercial supply**	PO	**If ≥ 18 years old:** 5 mg/dose BID^+		1 – 28	^Dose is BID. For example, if age < 18 years old, administer 2.4 mg/m^2/dose BID. The total daily dose is 4.8 mg/m^2/day, divided BID (maximum starting dose is 5 mg/dose BID). +See Section 4.3.3 for dose titration guidelines.
		If < 18 years old: 2.4 mg/m^2/dose (max 5 mg/dose) BID^+			
Nivolumab (IND#[redacted]) **Do not use commercial supply**	IV over 30 minutes, or per institutional guidelines	**If ≥ 18 years old:**	240 mg/dose **OR**	1, 15	**For patients ≥ 18 years old:** Either 240 mg/dose administered on Day 1 and 15 **OR** 480 mg/dose administered on Day 1 only.
			480 mg/dose	1 only	
		If < 18 years old: 3 mg/kg/dose		1, 15	**For patients < 18 years old:** Maximum dose is 240 mg/dose administered on Days 1 and 15.

Enter Cycle #: _____ **Ht** _____**cm** **Wt** _____**kg** **BSA** _____**m^2**

Date Due	Date Given	Day	Axitinib mg AM and mg PM	Nivolumab mg	Cycle 1 Studies	Cycles 2 - 26 studies
			Enter calculated dose above and actual dose administered below			
		1	mg mg	mg	a – o, p%, q – s	a – o, p%!, q – s
		2	mg mg			
		3	mg mg			
		4	mg mg			
		5	mg mg			
		6	mg mg			
		7	mg mg			
		8	mg mg		a*, c*, d – g	
		9	mg mg			
		10	mg mg			
		11	mg mg			
		12	mg mg			
		13	mg mg			
		14	mg mg			
		15	mg mg	mg#	a, c – g	(c – g)*
		16	mg mg			
		17	mg mg			
		18	mg mg			
		19	mg mg			
		20	mg mg			
		21	mg mg			
		22	mg mg		a*, c*, d – g	
		23	mg mg			
		24	mg mg			
		25	mg mg			
		26	mg mg			
		27	mg mg			
		28	mg mg			t
		29	Begin next cycle on Day 29 or when criteria to begin cycle are met, whichever occurs later. See Section 4.3.3. See Section 7.0 for end of treatment evaluations.		* For patients < 18 years of age only.	

Day 15 nivolumab does not apply to patients ≥ 18 years of age, receiving 480 mg/dose on Day 1 only.
% Required pharmacokinetics only applies to pediatric patients (age < 18 years old).
! Cycles 2 and 3 only. Patients should be instructed to hold the AM axitinib dose until after the pre-dose PK has been drawn.
See Section 5.0 for Dose Modifications for Toxicities.

4.3.2 Required Observations in Arm A: Axitinib + Nivolumab

All baseline studies must be performed prior to starting protocol therapy unless otherwise indicated below.

a. Physical Exam: Prior to each cycle, and additionally during Cycle 1:
   For patients < 18 years old, perform weekly
   For patients ≥ 18 years old, perform every other week

b. Height/Weight: Prior to each cycle.

c. CBC/diff/platelets: Prior to each dose of nivolumab, and additionally during Cycle 1:
   For patients < 18 years old, perform weekly
   For patients ≥ 18 years old, perform every other week

d. Creatinine, bilirubin: Prior to each dose of nivolumab, weekly during Cycle 1 only.

e. Electrolytes, BUN, Ca^{2+}, PO_4, Mg^{2+}: Prior to each dose of nivolumab, weekly during Cycle 1 only.

f. AST/ALT/Albumin: Prior to each dose of nivolumab, weekly during Cycle 1 only.

g. Blood Pressure: Prior to each dose of nivolumab, weekly during Cycle 1 only. For pediatric patients who are dose escalated, weekly monitoring for the first cycle at the higher dose will be required (See Section 5.2.5.4)

h. PT/INR: Prior to every odd-numbered cycle (e.g., Cycles 1, 3, 5, etc.).

i. TSH: Prior to every odd-numbered cycle (e.g., Cycles 1, 3, 5, etc.).

j. Urinalysis/Urine Protein/Creatinine: Prior to Cycles 1, 2, 3 and then prior to every odd-numbered cycle (e.g., Cycles 5, 7, 9, etc.).

k. Lipase: Prior to each cycle.

l. Pregnancy Test: Female patients of childbearing potential require a negative pregnancy test within 72 hours prior to starting treatment and then prior to every odd-numbered cycle (e.g., Cycles 3, 5, 7, etc.); sexually active patients must use an acceptable method of birth control.

m. ECG: Prior to every 4th cycle starting Cycle 1 (e.g., Cycles 1, 5, 9, etc.).

n. MUGA or ECHO: Prior to every 4th cycle starting Cycle 1 (e.g., Cycles 1, 5, 9, etc.).

o. GFR or Creatinine Clearance: Prior to every 4th cycle starting Cycle 1 (e.g., Cycles 1, 5, 9, etc.). See Appendix VII for GFR calculation.

p. Required Pharmacokinetics (for pediatric patients only): At 2, 4, and 6 hours post-axitinib AM dose during Cycle 1, Day 1. Additionally, pre-dose of axitinib on Day 1 of Cycles 2 and 3. For pediatric patients on Arm C that crossover to Arm A, required PK will be obtained at 2, 4 and 6 hours post-axitinib AM dose after the first dose of axitinib is given, and then pre-dose of axitinib on Days 1 of the second and third cycles of combination therapy received. **NOTE:** The first cycle of combination therapy after cross-over will be defined as the cycle for which > 14 days of axitinib is given, with Day 1 of Cycle 1 after cross-over defined as the day of first nivolumab dose during that cycle after axitinib is started or on the day axitinib is started if given concurrently. See Section 15.1 for complete details.

q. Immune biomarkers (patient consent is required): Before treatment initiation and before Day 1 of Cycles 2, 3, and 9 (within 72 hours prior to Day 1 dosing), and within 3 weeks after the last dose of study treatment. See Section 15.2.1 for complete details.

r. Tumor Tissue (patient consent is required): Before treatment initiation and at any time tumor tissue is obtained (i.e. surgery). See Section 15.2.2 for complete details.

s. Specimens for Banking (patient consent is required): See Section 15.2.3 for complete details.

t. Tumor Imaging: After Cycles 2, 4, 6, 9, 12, and then every 4 cycles; at relapse. For patients who cross-over from Arm C to Arm A at initial progression, then for the purpose

of imaging timing, the cycle number should restart at progression to "Cycle 1". See Section 16.2 for complete details.

This listing only includes evaluations necessary to answer the primary and secondary aims. OBTAIN OTHER STUDIES AS REQUIRED FOR GOOD CLINICAL CARE.

Comments
(Include any held doses, or dose modifications)

4.3.3 Treatment Details – Arm A: Axitinib + Nivolumab

Each cycle lasts 28 days (4 weeks). Absent disease progression or unacceptable toxicity, patients may continue on protocol therapy for up to 2 years duration or completion of 26 cycles, whichever comes first.

For patients who cross-over at disease progression on Arm C prior to Cycle 22, prior cycles received are included in total therapy calculations permitted on study.

Criteria to start each cycle: ANC ≥ 1000/µL, platelet count ≥ 75,000/µL without transfusion support. See Section 5.0 for other requirements related to any ongoing toxicities.

Axitinib: PO
Days: 1 – 28
Dose: Age-based dosing as follows:
If ≥ 18 years old: 5 mg/dose BID*
If < 18 years old: 2.4 mg/m^2/dose BID (maximum starting dose of 5 mg/dose)*. See Appendix IV for axitinib dosing nomogram and titrations.

NOTE: Dose is BID. For example, if age < 18 years old administer 2.4 mg/m^2/dose BID. The total daily dose is 4.8 mg/m^2/day, divided BID (maximum starting dose is 5 mg/dose BID).

Axitinib should be taken by mouth twice daily approximately 12 hours apart. Axitinib may be taken with or without food. Tablets should be administered whole and intact with a glass of water or other liquid; do not crush or cut tablets. If a dose is missed or vomited, the patient/subject should not try to repeat or "catch up" the dose. The next dose should be given at the next regularly scheduled time point.

Axitinib will be distributed by the Division of Cancer Treatment and Diagnosis (DCTD), NCI. Do not use commercial supply.

***Axitinib dose titration:**
Individual patient dose titration of axitinib (escalation from starting dose) is permitted on protocol therapy, at the discretion of the treating physician, if the following criteria are met for an individual patient:

1. Two consecutive cycles are completed at a given dose without any adverse reactions > Grade 2 (according to the Common Toxicity Criteria for Adverse Events [CTCAE]).
2. The patient is normotensive, and not receiving anti-hypertension medication.

For patients ≥ 18 years old, when a dose increase from 5 mg twice daily is recommended, the axitinib dose may be increased by 1 mg/dose twice daily (for example, from 5 mg twice daily to 6 mg twice daily, etc), up to a maximum of 10 mg twice daily. No more than 1 dose titration can occur in each 2-cycle period per the criteria above. Refer to the table in Section 5.2.1.1 for additional detail.

For patients < 18 years old, see Appendix IV for dose titration nomograms. No more than 1 dose titration can occur in each 2-cycle period per the criteria above. The maximum titration dose is as per the Dose Level 3 table in Appendix IV.

Nivolumab: IV over 30 minutes, or per institutional guidelines

Age	Dose and Days
≥ 18 years old	**Either** 240 mg/dose on Days 1 and 15 **OR** 480 mg/dose on Day 1 only
< 18 years old	3 mg/kg/dose (maximum 240 mg/dose) on Days 1 and 15

The risk of infusion reactions with nivolumab is low and no pre-medications are required. Monitoring for infusion reactions should be per institutional guidelines. Please refer to Section 5.3.2 for suggested infusion reaction management guidelines.

Nivolumab will be distributed by the Division of Cancer Treatment and Diagnosis (DCTD), NCI. Do not use commercial supply.

See Section 5.0 for Dose Modifications based on Toxicities.

Following completion of a cycle, begin next cycle on Day 29 or when criteria to begin cycle are met, whichever occurs later.

4.4 Arm B: Axitinib (For patients enrolled and randomized to Arm B prior to Amendment 2A) Closed to new accrual with Amendment 2A

4.4.1 Therapy Delivery Map – Arm B: Axitinib

Each cycle lasts 28 days (4 weeks). Absent disease progression or unacceptable toxicity, patients may continue on protocol therapy for up to 2 years duration or completion of 26 cycles, whichever comes first.
This TDM is on 3 pages. A copy of this TDM will be used for each cycle; please enter the cycle # below.

Patient COG ID number

DOB

Criteria to start each cycle: ANC ≥ 1000/µL, platelet count ≥ 75,000/µL without transfusion support. See Section 5.0 for other requirements related to any toxicities.

DRUG	ROUTE	DOSAGE	DAYS	IMPORTANT NOTES
Axitinib (IND#[redacted]) **Do not use commercial supply**	PO	**If ≥ 18 years old:** 5 mg/dose BID^+	1 – 28	^Dose is BID. For example, if age < 18 years old, administer 2.4 mg/m^2/dose BID. The total daily dose is 4.8 mg/m^2/day, divided BID (maximum starting dose is 5 mg BID). +See Section 4.4.3 for dose titration guidelines.
		If < 18 years old: 2.4 mg/m^2/dose (max 5 mg/dose) BID^+		

Enter Cycle #: **Ht** cm **Wt** kg **BSA** m^2

Date Due	Date Given	Day	Axitinib mg AM and mg PM	Cycle 1 Studies	Cycles 2 – 26 Studies
			Enter calculated dose above and actual dose administered below		
		1	mg mg	a – r	a – r
		2	mg mg		
		3	mg mg		
		4	mg mg		
		5	mg mg		
		6	mg mg		
		7	mg mg		
		8	mg mg	a*, c*, d – g	
		9	mg mg		
		10	mg mg		
		11	mg mg		
		12	mg mg		
		13	mg mg		
		14	mg mg		
		15	mg mg	a, c – g	g
		16	mg mg		
		17	mg mg		
		18	mg mg		
		19	mg mg		
		20	mg mg		
		21	mg mg		
		22	mg mg	a*, c*, d – g	
		23	mg mg		
		24	mg mg		
		25	mg mg		
		26	mg mg		
		27	mg mg		
		28	mg mg		s
		29	Begin next cycle on Day 29 or when criteria to begin cycle are met, whichever occurs later. See Section 4.4.3.	* For patients < 18 years of age only.	

See Section 5.0 for Dose Modifications for Toxicities. See Section 7.0 for end of treatment evaluations.

4.4.2 Required Observations in Arm B: Axitinib

All baseline studies must be performed prior to starting protocol therapy unless otherwise indicated below.

a. Physical Exam: Prior to each cycle, and additionally during Cycle 1:
   For patients < 18 years old, perform weekly
   For patients ≥ 18 years old, perform every other week

b. Height/Weight: Prior to each cycle.

c. CBC/diff/platelets: Prior to each cycle, and additionally during Cycle 1:
   For patients < 18 years old, perform weekly
   For patients ≥ 18 years old, perform every other week

d. Creatinine, bilirubin: Prior to each cycle, weekly during Cycle 1 only.

e. Electrolytes, BUN, Ca^{2+}, PO_4, Mg^{2+}: Prior to each cycle, weekly during Cycle 1 only.

f. AST/ALT/Albumin: Prior to each cycle, weekly during Cycle 1 only.

g. Blood Pressure: Every other week, weekly during Cycle 1 only. For pediatric patients who are dose escalated, weekly monitoring for the first cycle at the higher dose will be required (See Section 5.2.5.4)

h. PT/INR: Prior to every odd-numbered cycle (e.g., Cycles 1, 3, 5, etc.).

i. TSH: Prior to every odd-numbered cycle (e.g., Cycles 1, 3, 5, etc.).

j. Urinalysis/Urine Protein/Creatinine: Prior to Cycles 1, 2, 3, and then prior to every odd-numbered cycle (e.g., Cycles 5, 7, 9 etc.).

k. Lipase: Prior to each cycle.

l. Pregnancy Test: Female patients of childbearing potential require a negative pregnancy test within 72 hours prior to starting treatment and then prior to every odd-numbered cycle (e.g., Cycles 3, 5, 7, etc.); sexually active patients must use an acceptable method of birth control.

m. ECG: Prior to every 4th cycle starting Cycle 1 (e.g., Cycles 1, 5, 9, etc.).

n. MUGA or ECHO: Prior to every 4th cycle starting Cycle 1 (e.g., Cycles 1, 5, 9, etc.).

o. GFR or Creatinine Clearance: Prior to every 4th cycle starting Cycle 1 (e.g., Cycles 1, 5, 9, etc.). See Appendix VII for GFR calculation.

p. Immune biomarkers (patient consent is required): Before treatment initiation and before Day 1 of Cycles 2, 3, and 9 (within 72 hours prior to Day 1 dosing), and within 3 weeks after the last dose of study treatment. See Section 15.2.1 for complete details.

q. Tumor Tissue (patient consent is required): Before treatment initiation and at any time tumor tissue is obtained (i.e. surgery). See Section 15.2.2 for complete details.

r. Specimens for Banking (patient consent is required): See Section 15.2.3 for complete details.

s. Tumor Imaging: After Cycles 2, 4, 6, 9, 12, and then every 4 cycles; at relapse. See Section 16.2 for complete details.

This listing only includes evaluations necessary to answer the primary and secondary aims. OBTAIN OTHER STUDIES AS REQUIRED FOR GOOD CLINICAL CARE.

Comments
(Include any held doses, or dose modifications)

4.4.3 Treatment Details – Arm B: Axitinib

IMPORTANT: Arm B is closed to new patients as of Amendment 2A. For patients who were enrolled and randomized to Arm B prior to Amendment 2A, please refer to the treatment details below.

Each cycle lasts 28 days (4 weeks). Absent disease progression or unacceptable toxicity, patients may continue on protocol therapy for up to 2 years duration or completion of 26 cycles, whichever comes first.

Criteria to start each cycle: ANC ≥ 1000/μL, platelet count ≥ 75,000/μL without transfusion support. See Section 5.0 for other requirements related to any toxicities.

Axitinib: PO
Days: 1 – 28
Dose: Age-based dosing as follows:
If ≥ 18 years old: 5 mg/dose BID*
If < 18 years old: 2.4 mg/m^2/dose BID (maximum starting dose of 5 mg/dose)*. See Appendix IV for axitinib dosing nomogram and titrations.

NOTE: Dose is BID. For example, if < 18 years old administer 2.4 mg/m^2/dose BID. The total daily dose is 4.8 mg/m^2/day, divided BID (maximum starting dose is 5 mg BID).

Axitinib should be taken by mouth twice daily approximately 12 hours apart. Axitinib may be taken with or without food. Tablets should be administered whole and intact with a glass of water or other liquid; do not crush or cut tablets. If a dose is missed or vomited, the patient/subject should not try to repeat or "catch up" the dose. The next dose should be given at the next regularly scheduled time point.

Axitinib will be distributed by the Division of Cancer Treatment and Diagnosis (DCTD), NCI. Do not use commercial supply.

***Axitinib dose titration:**
Individual patient dose titration of axitinib (escalation from starting dose) is permitted on protocol therapy, at the discretion of the treating physician, if the following criteria are met for an individual patient:

1. Two consecutive cycles are completed at a given dose without any adverse reactions > Grade 2 (according to the Common Toxicity Criteria for Adverse Events [CTCAE]).
2. The patient is normotensive, and not receiving anti-hypertension medication.

For patients ≥ 18 years old, when a dose increase from 5 mg twice daily is recommended, the axitinib dose may be increased by 1 mg/dose twice daily (for example, from 5 mg twice daily to 6 mg twice daily, etc), up to a maximum of 10 mg twice daily. No more than 1 dose titration can occur in each 2-cycle period per the criteria above. Refer to the table in Section 5.2.1.1 for additional detail.

For patients < 18 years old, see Appendix IV for dose titration nomograms. No more than 1 dose titration can occur in each 2-cycle period per the criteria above. The maximum titration dose is as per the Dose Level 3 table in Appendix IV.

See Section 5.0 for Dose Modifications based on Toxicities.

Following completion of a cycle, begin next cycle on Day 29 or when criteria to begin cycle are met, whichever occurs later.

4.5 Arm C: Nivolumab

4.5.1 Therapy Delivery Map – Arm C: Nivolumab Each cycle lasts 28 days (4 weeks). Absent disease progression or unacceptable toxicity, patients may continue on protocol therapy for up to 2 years duration or completion of 26 cycles, whichever comes first. This TDM is on 3 pages. A copy of this TDM will be used for each cycle; please enter the cycle # below.	_____ Patient COG ID number _____ DOB

Criteria to start each cycle: ANC ≥ 1000/μL, platelet count ≥ 75,000/μL without transfusion support.
See Section 5.0 for other requirements related to any ongoing toxicities.

DRUG	ROUTE	DOSAGE		DAYS	IMPORTANT NOTES
Nivolumab (IND#[redacted]) **Do not use commercial supply**	IV over 30 minutes, or per institutional guidelines	**If ≥ 18 years old:**	240 mg/dose **OR**	1, 15	**For patients ≥ 18 years old:** Either 240 mg/dose administered on Day 1 and 15 **OR** 480 mg/dose administered on Day 1 only.
			480 mg/dose	1 only	
		If < 18 years old: 3 mg/kg/dose		1, 15	**For patients < 18 years old:** Maximum dose is 240 mg/dose administered on Days 1 and 15.

Enter Cycle #: _____ **Ht** _____**cm** **Wt** _____**kg** **BSA** _____**m²**

Date Due	Date Given	Day	Nivolumab ___mg	Cycle 1 Studies	Cycles 2 – 26 Studies
			Enter calculated dose above and actual dose administered below		
		1	___mg	a – q	a - q
		…			
		8		a*, c*, d – f	
		…			
		15	___mg[#]	a, c – f	(c – f)*
		…			
		22		a*, c*, d – f	
		…			
		28			r
		29	Begin next cycle on Day 29 or when criteria to begin cycle are met, whichever occurs later. See Section 4.5.3. See Section 7.0 for end of treatment evaluations.	* For patients < 18 years of age only.	

[#] Day 15 nivolumab does not apply to patients ≥ 18 years of age, receiving 480 mg/dose on Day 1 only.
See Section 5.0 for Dose Modifications for Toxicities.

4.5.2 Required Observations in Arm C: Nivolumab

All baseline studies must be performed prior to starting protocol therapy unless otherwise indicated below.

a. Physical Exam: Prior to each cycle, and additionally during Cycle 1:
   For patients < 18 years old, perform weekly
   For patients ≥ 18 years old, perform every other week

b. Height/Weight: Prior to each cycle.

c. CBC/diff/platelets: Prior to each dose of nivolumab, and additionally during Cycle 1:
   For patients < 18 years old, perform weekly
   For patients ≥ 18 years old, perform every other week

d. Creatinine, bilirubin: Prior to each dose of nivolumab, weekly during Cycle 1 only.

e. Electrolytes, BUN, Ca^{2+}, PO_4, Mg^{2+}: Prior to each dose of nivolumab, weekly during Cycle 1 only.

f. AST/ALT/Albumin: Prior to each dose of nivolumab, weekly during Cycle 1 only.

g. PT/INR: Prior to every odd-numbered cycle (e.g., Cycles 1, 3, 5, etc.).

h. TSH: Prior to every odd-numbered cycle (e.g., Cycles 1, 3, 5, etc.).

i. Urinalysis/Urine Protein/Creatinine: Prior to Cycles 1, 2, 3 and then prior to every odd-numbered cycle (e.g., Cycles 5, 7, 9, etc.).

j. Lipase: Prior to each cycle.

k. Pregnancy Test: Female patients of childbearing potential require a negative pregnancy test within 72 hours prior to starting treatment and then prior to every odd-numbered cycle (e.g., Cycles 3, 5, 7, etc.); sexually active patients must use an acceptable method of birth control.

l. ECG: Prior to every 4th cycle starting Cycle 1 (e.g., Cycles 1, 5, 9, etc.).

m. MUGA or ECHO: Prior to every 4th cycle starting Cycle 1 (e.g., Cycles 1, 5, 9, etc.).

n. GFR or Creatinine Clearance: As clinically indicated. See Appendix VII for GFR calculation.

o. Immune biomarkers (patient consent is required): Before treatment initiation and before Day 1 of Cycles 2, 3, and 9 (within 72 hours prior to Day 1 dosing), and within 3 weeks after the last dose of study treatment. See Section 15.2.1 for complete details.

p. Tumor Tissue (patient consent is required): Before treatment initiation and at any time tumor tissue is obtained (i.e. surgery). See Section 15.2.2 for complete details.

q. Specimens for Banking (patient consent is required): See Section 15.2.3 for complete details.

r. Tumor Imaging: After Cycles 2, 4, 6, 9, 12, and then every 4 cycles; at relapse. See Section 16.2 for complete details.

This listing only includes evaluations necessary to answer the primary and secondary aims. OBTAIN OTHER STUDIES AS REQUIRED FOR GOOD CLINICAL CARE.

Comments
(Include any held doses, or dose modifications)

4.5.3 Treatment Details – Arm C: Nivolumab

Each cycle lasts 28 days (4 weeks). Absent disease progression or unacceptable toxicity, patients may continue on protocol therapy for up to 2 years duration or completion of 26 cycles, whichever comes first.

Criteria to start each cycle: ANC ≥ 1000/μL, platelet count ≥ 75,000/μL without transfusion support. See Section 5.0 for other requirements related to any ongoing toxicities.

Nivolumab: IV over 30 minutes or per institutional guidelines

Age	Dose and Days
≥ 18 years old	**Either** 240 mg/dose on Days 1 and 15 **OR** 480 mg/dose on Day 1 only
< 18 years old	3 mg/kg/dose (maximum 240 mg/dose) on Days 1 and 15

The risk of infusion reactions with nivolumab is low and no pre-medications are required. Monitoring for infusion reactions should be per institutional guidelines. Please refer to Section 5.3.2 for suggested infusion reaction management guidelines.

Nivolumab will be distributed by the Division of Cancer Treatment and Diagnosis (DCTD), NCI. Do not use commercial supply.

See Section 5.0 for Dose Modifications based on Toxicities.

Following completion of a cycle, begin next cycle on Day 29 or when criteria to begin cycle are met, whichever occurs later.

Patients on Arm C that meet protocol defined criteria of disease progression prior to Cycle 22 of therapy, may cross-over and receive Arm A (combination) therapy. Total therapy received on study AREN1721, either on Arm A, Arm C, or for patients that cross-over, is not to exceed 26 cycles total or 2 years, whichever comes first.

5.0 DOSE MODIFICATIONS FOR TOXICITIES

5.1 Definitions of Dose-Limiting Toxicities (DLT)

DLT will be defined as any of the following events that are possibly, probably, or definitely attributable to protocol therapy.

NOTE: Dose-limiting hematological and non-hematological toxicities are defined differently. The Study Chair should be notified of any suspected or confirmed DLT.

5.1.1 Hematological DLT

5.1.1.1 Hematological dose-limiting toxicity is defined as:

- Grade 4 thrombocytopenia (platelet count < 25,000/μL) or Grade 4 neutropenia for > 7 days (see Section 5.2), not due to malignant infiltration.

5.1.1.2 Other hematological dose-limiting toxicities:

- Any Grade 2 arterial thromboembolic events (including cerebrovascular ischemia, peripheral or visceral arterial ischemia).
- Any ≥ Grade 3 venous thromboembolic event.
- Any thrombotic event requiring systemic anti-coagulation.
- Any ≥ Grade 2 hemorrhage.

5.1.2 Non-hematological DLT

5.1.2.1 Any Grade 3 or Grade 4 non-hematological toxicity attributable to the investigational drug with the specific **exclusion** of:

- Grade 3 proteinuria (urine protein/ creatinine (P/C) ratio > 1.9 for age < 18; urine protein ≥ 3.5 g/24 hours for age 18 and greater) unless it is confirmed with a second measurement within 72 hours.
- Grade 3 liver enzyme elevation, including AST/ALT that returns to levels that meet eligibility criteria within 7 days of study drug interruption and that does not recur upon study drug rechallenge.
- Grade 3 GGT, if checked. (Note: monitoring GGT is not required for this study)
- Grade 3 serum electrolyte elevation that returns to baseline within 7 days and does not require systemic immunosuppression.
- Grade 3 asymptomatic lipase elevation that resolves to meet the eligibility criterion within 7 days of study drug interruption and that does not recur upon study drug re-challenge.
- Grade 3 or 4 amylase or lipase abnormalities that are not associated with diabetes mellitus (DM), associated liver or gall bladder inflammation clinical manifestations of pancreatitis and which decrease to ≤ Grade 2 within 7 days.
- Grade 3 diarrhea ≤ 3 days duration.
- Grade 3 nausea and vomiting of less < 3 days duration.
- Grade 3 or 4 fever < 5 days duration.
- Grade 3 infection < 5 days duration.
- Grade 3 rash/oral lesion that resolves to Grade ≤ 1 within 7 days.
- Fever greater than 40°C of ≤ 24 hr duration.
- Grade 3 fatigue that resolves to Grade ≤ 2 within 7 days.

- Grade 3 creatinine increased that resolves to Grade ≤ 1 or baseline within 7 days.
- Grade 3 pleural effusion that resolves per Section 5.2.6.
- Grade 3 hypophosphatemia, hypokalemia, hypocalcemia or hypomagnesemia responsive to oral supplementation.

5.1.2.2 Grade 2 uveitis, eye pain, or blurred vision that does not respond to topical therapy and does not improve to Grade 1 prior to the next scheduled dose.

5.1.2.3 Grade 2 non-hematological toxicity requiring systemic immunosuppressive therapy, including but not limited to, autoimmunity of the lung, heart, kidney, bowel, CNS, pituitary or eye, with the specific exclusion of:

a. Grade 2 pleural effusion that resolves per Section 5.2.6.
b. Drugs will be held for Grade 2 cardiac dysfunction pending evaluation.

5.1.2.4 Grade 2 endocrine toxicity requiring hormone replacement, with the exception of Grade 2 hypothyroidism, thyroiditis, and thyroid dysfunction adequately managed with thyroid hormone replacement (see Section 5.3).

5.1.2.5 Grade 2 adrenal insufficiency.

5.1.2.6 Grade 2 colitis or Grade 2 diarrhea attributable to protocol therapy that persists for > 7 days.

5.1.2.7 Any non-hematological toxicity requiring > 7 days delay in therapy.
NOTE: Allergic reactions that necessitate discontinuation of study drug will not be considered a DLT.

5.1.2.8 Dose-limiting hypertension

- Any Grade 4 hypertension.
- Any Grade 3 hypertension that persists for > 14 days despite adequate antihypertensive treatment.

5.1.2.9 Any Grade 2 non-hematological toxicity that persists for ≥ 7 days and is considered sufficiently medically significant or sufficiently intolerable by patients that it requires treatment interruption.

5.2 Dose Modifications for Axitinib

5.2.1 Axitinib Dosing Nomogram

5.2.1.1 For patients ≥ 18 years of age

Dose Level	Axitinib Dose (mg PO BID)
-3[#]	2
-2	3
-1	4
1*	**5**
2	6
3	7
4	8
5	9
6	10

* Starting dose

[#] If a patient was most recently dosed at the lowest dose level and requires a subsequent dose reduction, the patient must be removed from protocol therapy.

5.2.1.2 For patients < 18 years of age

See Appendix IV for dosing nomograms and titrations.

Dose Level	Axitinib Dose (mg/m^2/dose PO BID)
-1[#]	1.8 (max 4 mg/dose BID)
1*	**2.4 (max 5 mg/dose BID)**
2	See dose titration in Appendix IV
3	See dose titration in Appendix IV

* Starting dose

[#] If a patient was most recently dosed at the lowest dose level and requires a subsequent dose reduction, the patient must be removed from protocol therapy.

5.2.2 It is recognized that to avoid high grade toxicities, periodic breaks from axitinib dosing may benefit patients. In general, such breaks of up to 7 days per cycle will permitted at the discretion of the treating physician. Such breaks may be considered for non-DLT related recurrent toxicities impacting a patient's quality of life.

5.2.3 If a patient experiences a Grade 4 neutropenia or Grade 4 thrombocytopenia, axitinib will be withheld. Counts should be checked twice weekly until ≤ Grade 3.

5.2.3.1 If the toxicity resolves to meet eligibility or baseline within 7 days of drug discontinuation, axitinib may be restarted either at the same dose level or at one dose level lower (see Section 5.2.1) at the discretion of the treating physician. For delays of more than 7 and up to 21 days, dose reduction is required. Doses reduced for toxicity will not be re-escalated, even if there is minimal or no toxicity at the lower dose level.

5.2.3.2 If toxicity does not resolve to meet eligibility or baseline within 21 days of drug discontinuation, the patient must be removed from protocol therapy.

5.2.4 If a patient experiences Grade 3 or 4 non-hematologic toxicity, axitinib should be held until toxicity resolves to ≤ Grade 2. If the toxicity resolves to ≤ Grade 2 within 7 days, axitinib may be restarted either at the same dose level or at one dose level lower (see Section 5.2.1) at the discretion of the treating physician. For delays of more than 7 and up to 21 days, dose reduction is required. For delays of more than 21 days, the patient must be removed from protocol therapy.

5.2.5 Dose Modifications for Hypertension:

5.2.5.1 Baseline blood pressure (BP) is defined as the blood pressure obtained at the examination used for study enrollment. This baseline BP should be obtained as follows: (1) Obtain 2 serial blood pressures from the same extremity with the patient in the same position that are separated by at least 1 hour. Avoid using the lower extremity if possible. (2) The baseline BP is the average of the systolic measurements over the average of the diastolic measurements.

5.2.5.2 The upper limit of normal (ULN) is defined as a BP equal to the 95th percentile for age, height, and gender (see Appendix III) for patients < 18 years old, and 150/90 mmHg for patients ≥ 18 years old.

- The NCI CTCAE will be utilized to determine the grade of hypertension for reporting purposes.
- Elevated BP measurements should be repeated on the same day to confirm the elevation. Patients with elevated BP should have BP measurements performed at least twice weekly until BP is ≤ ULN.
- Elevation in either systolic or diastolic blood pressure should be considered when following the algorithms below.
- Hypertension should be managed with appropriate anti-hypertensive agent(s) as clinically indicated. It is strongly recommended that nephrology or cardiology be consulted in the evaluation and management of hypertension.

5.2.5.3 **Adults (≥ 18 years of age):**

Patients/families will self-monitor BP at home twice weekly and will inform their physicians in the event of systolic BP ≥ 140 mmHg or diastolic BP ≥ 90 mmHg. In such instances, antihypertensive treatment will start or the dose of antihypertensives will be increased per physician discretion. Table 1 below provides guidelines for monitoring and managing axitinib-related hypertension in adult patients. If the patient was already on maximal antihypertensive treatment, the axitinib dose will be reduced by one dose level (see Section 5.2.1).

Table 1. Recommended Hypertension Monitoring and Management for Adult Patients

CTCAE Grade	Antihypertensive Therapy	Blood Pressure Monitoring	Dose Modification
Grade 1 – Pre-hypertension Systolic 120-139 mmHg Diastolic 80-89 mmHg		Standard	No change
Grade 2 – Moderate Systolic 140-159 mmHg Diastolic 90-99 mmHg	1) Initiate LA DHP CCB[#] treatment and if needed, after 24-48 hr Rx, increase dose in stepwise fashion every 24-48 hrs until BP is controlled or at max dose of Rx. 2) If BP still not controlled, add another antihypertensive Rx, a BB[!], ACEI[^], or ARB[*]; increase dose of this drug as described in Step 1. 3) If BP still not controlled, add 3rd drug from the list of hypertensives in Step 2; increase dose of this drug as described in Step 1. 4) If BP still not controlled, consider either 1 dose reduction of axitinib (see Section 5.2.1) or stopping axitinib.*	BP should be monitored as recommended by the treating physician	No change except as described in Step 4
Grade 3 – Severe Systolic ≥ 160 mmHg Diastolic ≥ 100 mmHg	HOLD axitinib* until systolic ≤ 159 mmHg and diastolic ≤ 99 mmHg. BP management is identical to that for Grade 2 above **with 2 major exceptions:** **1) If systolic > 180 mmHg or diastolic > 110 mmHg and the patient is symptomatic:** optimal management with intensive IV support in ICU; STOP axitinib.* **2) If systolic > 180 mmHg or diastolic > 110 mmHg and the patient is asymptomatic:** 2 new	BP should be monitored as recommended by the treating physician **unless the patient is symptomatic with systolic > 180 mmHg or diastolic > 110 mmHg, in which case monitoring should be intensive.**	HOLD axitinib* until systolic ≤ 159 mmHg and diastolic ≤ 99 mmHg. In most circumstances, if BP cannot be controlled after an optimal trial of antihypertensive medications, consider either 1 dose reduction of axitinib (see Section 5.2.1) or stopping axitinib.* **If the patient requires hospitalization for**

	antihypertensives must be given together in Step 1 (and dose escalated appropriately as in Step 1).		**management of symptomatic systolic > 180 mmHg or diastolic > 110 mmHg,** permanently discontinue axitinib, or if BP is controlled, restart axitinib at 1 dose level lower.*

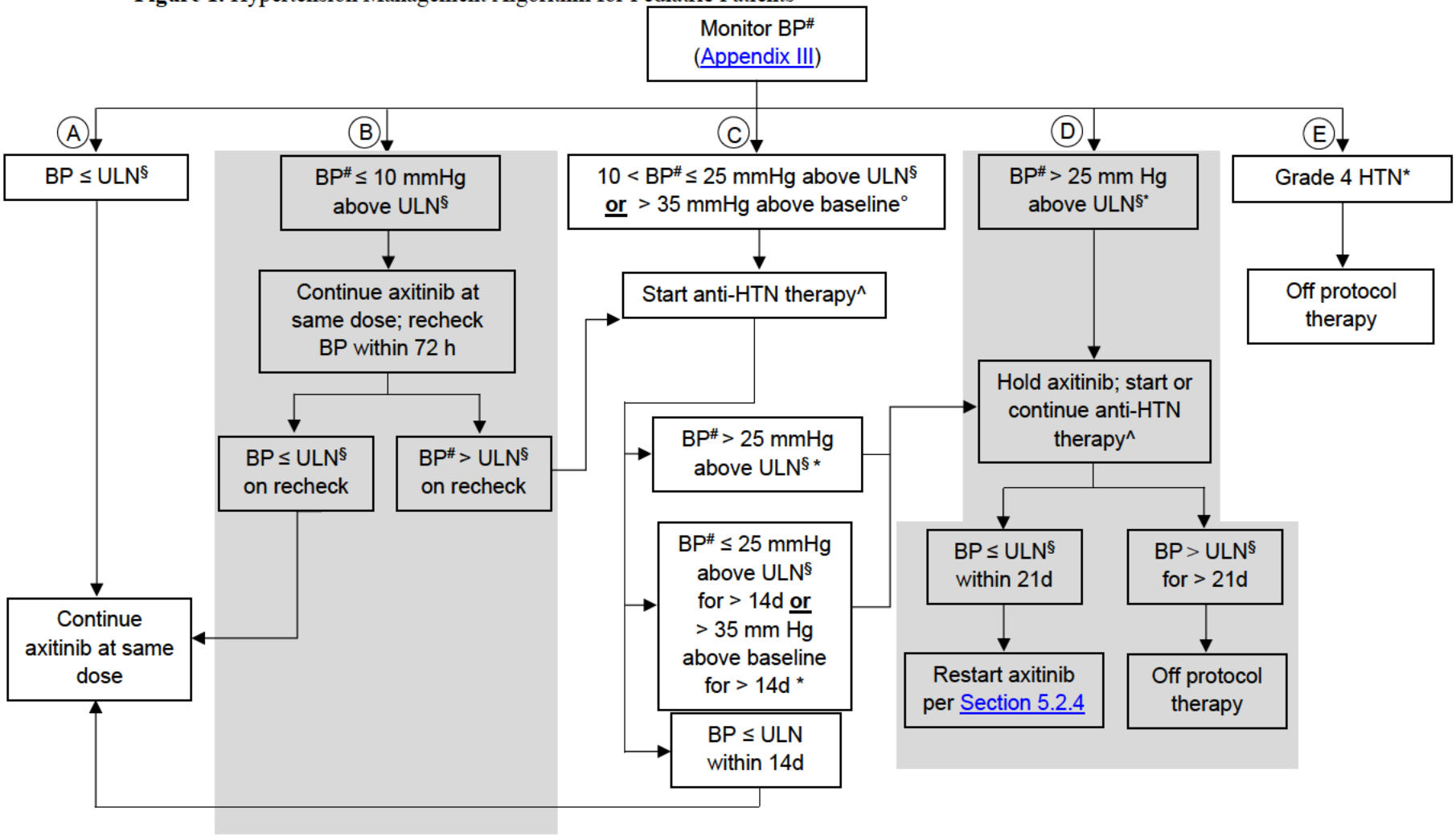
LA DHP CCB [#]: long-acting dihydropyridine calcium channel blocker
BB[!]: beta-blocker
ACEI[^]: angiotensin converting enzyme inhibitor
ARB[*]: angiotensin II receptor blockers
***NOTE:** Stopping or reducing the dose of axitinib is expected to cause a decrease in BP. The treating physician should monitor the patient for hypotension and adjust the number and dose of antihypertensive medication(s) accordingly.

5.2.5.4 **Pediatrics (< 18 years of age):**

Monitoring for children on axitinib will occur weekly during Cycle 1 (the period during which development of hypertension is most evident), and every other week thereafter. For patients who are dose escalated, weekly monitoring for the first cycle at the higher dose will also be required. Blood pressure will be measured with an appropriate sized cuff at rest. This can be monitored in the clinic or by alternative monitoring (home, pediatrician, alternative).

The algorithm in Figure 1 below provides guidelines for managing axitinib-related hypertension in pediatric patients.

Figure 1. Hypertension Management Algorithm for Pediatric Patients



Elevations in BP are based on systolic or diastolic pressures.

Elevated blood pressure (BP) measurements should be repeated on the same day to confirm the elevation. Patients with elevated BP at any time should have BP measurements performed at least twice weekly until BP is within the ULN.

§ ULN (Upper Limit of Normal) is a BP equal to the 95th percentile from age, height, and gender-appropriate normal values (Appendix III).

* If BP > 25 mmHg above ULN for age (verified) or Grade 4 hypertension (HTN) at any time, hold axitinib. Axitinib should also be held for BP ≤ 25 mmHg above the ULN for > 14 days or 35 mmHg above baseline for > 14 days. Antihypertensive agents can be used to control hypertension as clinically indicated after axitinib is held. **NOTE:** When axitinib is held and the patient is on antihypertensive treatment, the patient should be closely monitored for hypotension.

^ Antihypertensive therapy should be prescribed as clinically indicated, including the use of multiple anti-hypertensive agents.

° Baseline BP is defined in Section 5.2.5.1.

Arm A of algorithm:

- If blood pressure (BP) ≤ 95% for age, height, and gender, continue axitinib at the same dose.

Arm B of algorithm:

- If BP ≤ 10 mm Hg above the ULN for age, height, and gender, continue axitinib at the same dose and recheck the BP within 72 hours.
  - If the BP is ≤ ULN on recheck, continue axitinib at the same dose.
- If the BP remains above the ULN on recheck, then start antihypertensive therapy (see Figure 1) and follow Arm C of the algorithm from the point that anti-hypertensive therapy is started.

Arm C of algorithm:

- If BP is 11 to 25 mm Hg above the 95% for age, height, and gender or > 35 mmHg above baseline, start anti-hypertensive therapy (see Figure 1), continue axitinib at the same dose, and monitor BP at least twice weekly.
  - If the BP returns to ≤ ULN within 14 days, continue axitinib at the same dose and continue anti-hypertensive therapy.
  - If the BP remains elevated ≤ 25 mm Hg above the 95% or > 35 mm Hg above baseline for more than 14 days after the initiation of antihypertensive therapy, **hold** axitinib, monitor BP at least every 3 days, and follow Arm D of the algorithm from the point that axitinib is held. **NOTE:** When axitinib is held and the patient is on antihypertensive treatment, the patient should be closely monitored for hypotension. The antihypertensive therapy should be continued until the BP is less than the ULN.
  - If the BP increases to > 25 mm Hg above the ULN despite anti-hypertensive therapy, **hold** axitinib, but continue the anti-hypertensive agent(s). **NOTE:** When axitinib is held and the patient is on antihypertensive treatment, the patient should be closely monitored for hypotension. Monitor the BP as clinically indicated and follow Arm D of the algorithm from the point that axitinib is held.

Arm D of algorithm:

- If BP is > 25 mm Hg above the 95% for age, height, and gender **hold** axitinib, monitor BP and administer anti-hypertensive therapy as clinically indicated. **Note:** When axitinib is held and the patient is on antihypertensive treatment, the patient should be closely monitored for hypotension.
  - If the BP returns to ≤ ULN within 21 days, axitinib may be restarted as described in Section 5.2.4.
  - If the BP is > ULN for > 21 days, the patient must be removed from protocol therapy.

Arm E of algorithm:

- If the participant develops Grade 4 hypertension, **discontinue** axitinib, monitor BP and administer anti-hypertensive therapy as clinically indicated. The patient must be removed from protocol therapy. **NOTE:** When axitinib is held and the patient is on antihypertensive treatment, the patient should be closely monitored for hypotension.

5.2.6 Dose Modifications and Adverse Event Management for Pleural Effusion and Ascites:

Pleural effusion or ascites	Non-life-threatening (Grade < 4) pleural effusion or ascites	• Treat with appropriate supportive care, which may include: non-investigational diuretics, thoracentesis, chest tube drainage, paracentesis or pleurodesis. • For Grade 1 pleural effusion or Grade 1 or 2 ascites, monitor with physical exam and consider additional imaging. • For Grade ≥ 2 pleural effusion or grade 3 ascites, initiate methylprednisolone (2 mg/kg/day IV) or oral equivalent with attempt to taper over 7-10 days after a minimum of 24 hours of treatment. • If chest tube drainage, pleurodesis or paracentesis is required, protocol therapy should be held until at least 2 days after the procedure or chest tube removal and the patient's condition is stable. • If pleural effusion or ascites resolves or is managed to achieve Grade ≤ 1 and steroids are discontinued, protocol therapy may proceed without dose reduction. If pleural effusion or ascites is not resolved/managed to Grade ≤ 1 and steroids are not discontinued within 28 days of next scheduled dose of nivolumab, discontinue protocol therapy
	Grade 4 or life-threatening pleural effusion or ascites	• Institute emergency measures per institutional guidelines • Initiate methylprednisolone 2 mg/kg/day IV or oral equivalent with plan to taper as tolerated. • Permanently discontinue protocol therapy

5.2.7 Dose Modifications for Proteinuria:

5.2.7.1 **Adults**

Axitinib treatment will be held in patients with greater than 2 g proteinuria per 24 hours. If measurements of total protein and creatinine clearance become less than 2 grams proteinuria per 24 hours within 21 days, axitinib may be restarted as described in Section 5.2.4. For delays of more than 21 days, the patient must be removed from protocol therapy.

5.2.7.2 **Pediatrics (< 18 years of age)**

If the urine protein/creatinine (P/C) ratio is ≤ 1.9, continue axitinib at the same dose. If patient has Grade 3 proteinuria (P/C ratio > 1.9), a second measurement should be obtained within 72 hours. If the second measurement confirms Grade 3 proteinuria (P/C ratio > 1.9), hold axitinib and re-assess weekly. If the P/C ratio decreases to ≤ 1.9 within 21 days, axitinib may be restarted as described in Section 5.2.4. Monitor the UPC weekly for 2 consecutive weeks once protocol therapy resumes. For delays of more than 21 days, the patient must be removed from protocol therapy.

5.2.8 Dose Modifications for Cardiac Toxicity:

Patients who experience ≥ Grade 3 left ventricular systolic dysfunction must be removed from protocol therapy and referral to a cardiologist is recommended.

5.2.9 Dose Modifications for Diarrhea:
If Grade 3 (> 3 day duration) or Grade 4 therapy-associated diarrhea is experienced by a patient despite maximal use of anti-diarrheal medications the dose of axitinib should be reduced by one dose level for subsequent cycles (see Section 5.2.1).

5.3 Dose Modifications for Nivolumab

Adverse events (both non-serious and serious) associated with nivolumab exposure may represent an immunologic etiology. These adverse events may occur shortly after the first dose or several months after the last dose of treatment. Nivolumab must be withheld for drug-related toxicities and severe or life-threatening AEs as per Table 2 below. Please also refer to Appendix V for suggested management guidelines. Please note some of the guidelines include references to medications which may not be appropriate for patients < 18 years of age.

Table 2. Dose Modification Guidelines for Nivolumab-Related Adverse Events

Toxicity	Hold Treatment for Grade	Timing for Restarting Treatment	Treatment Discontinuation
Diarrhea/Colitis (age ≥ 18 years)	2-3	Toxicity resolves to Grade 0-1	Toxicity does not resolve within 6 weeks of last dose or inability to reduce corticosteroid to 0.15 mg/kg (up to 10 mg) or less of prednisone or equivalent per day within 6 weeks
	4	Permanently discontinue	Permanently discontinue
Diarrhea (age < 18 years)	2-3 if not reversible within 7 days and related to drug	Toxicity resolves to Grade 0-1 (evaluate for colitis)	Toxicity does not resolve within 6 weeks of last dose or inability to reduce corticosteroid to 0.15 mg/kg (up to 10 mg) or less of prednisone or equivalent per day within 6 weeks
	4	Permanently discontinue	Permanently discontinue
AST, ALT, or Increased Bilirubin (age ≥ 18 years)	2	Toxicity resolves to Grade 0-1	Toxicity does not resolve within 6 weeks of last dose
	3-4	Permanently discontinue (see exception below)[a]	Permanently discontinue
AST, ALT (age < 18 years)	2-3 if not reversible within 7 days and related to drug	Toxicity resolves to Grade 0-1 (monitor AST/ALT at least twice per week until resolution)	Toxicity does not resolve within 6 weeks of last dose
	4	Permanently discontinue (see exception below)[a]	Permanently discontinue
Type 1 diabetes mellitus (if new onset) or Hyperglycemia[b]	T1DM or 3-4	Hold nivolumab for new onset Type 1 diabetes mellitus or Grade 3-4 hyperglycemia associated with evidence of beta cell failure For Grade 2 or higher pancreatitis-associated diabetes, a patient will come off protocol therapy.	Resume nivolumab when patients are clinically and metabolically stable For Grade 2 or higher pancreatitis-associated diabetes, a patient will come off protocol therapy.
Hypophysitis	2-4	Toxicity resolves to Grade 0-1. Therapy with nivolumab can be continued while endocrine replacement therapy is instituted.	Toxicity does not resolve within 6 weeks of last dose or inability to reduce corticosteroid to 0.15 mg/kg (up to 10 mg) or less of prednisone or equivalent per day within 6 weeks.
Hyperthyroidism	3	Toxicity resolves to Grade 0-1	Toxicity does not resolve within 6 weeks of last dose or inability to reduce corticosteroid to 0.15 mg/kg (up to 10 mg) or less of prednisone or equivalent per day within 6 weeks.
	4	Permanently discontinue	Permanently discontinue

Toxicity	Hold Treatment for Grade	Timing for Restarting Treatment	Treatment Discontinuation
Hypothyroidism		Therapy with nivolumab can be continued while thyroid replacement therapy is instituted.	Therapy with nivolumab can be continued while thyroid replacement therapy is instituted.
Infusion Reaction	2[c]	Toxicity resolves to Grade 0-1	Permanently discontinue if toxicity develops despite adequate premedication
	3-4	Permanently discontinue	Permanently discontinue
Cardiac Toxicities (Including CHF, LV systolic dysfunction, Myocarditis, CPK, and troponin)	1	Hold dose pending evaluation and observation. (*Patients with evidence of myositis without myocarditis may be treated according as "other event") Note: The optimal treatment regimen for immune mediated myocarditis has not been established. Since this toxicity has caused patient deaths, an aggressive approach is recommended. Evaluate for signs and symptoms of CHF, ischemia, arrhythmia or myositis. Obtain history, EKG, CK (for concomitant myositis), CK-MB. Repeat troponin, CK, and EKG within 2-3 days. If troponin and labs normalize may resume therapy. If labs worsen or symptoms develop then treat as below. Hold drug pending evaluation.	Toxicity does not resolve within 6 weeks of last dose
	2, 3, 4 (Suspected myocarditis)	Hold dose. Admit to hospital. Cardiology consult. Rule out myocardial infarction and other causes of cardiac disease. Cardiac Monitoring. Cardiac Echo. Consider cardiac MRI and cardiac biopsy. Initiate high dose methylprednisolone. If no improvement within 24 hours, add either infliximab, ATG or tacrolimus. Resume therapy if there is a return to baseline and myocarditis is excluded or considered unlikely.	Toxicity does not resolve within 6 weeks of last dose
	2, 3, 4 (myocarditis confirmed)		Permanently Discontinue. Admit to Critical Care Unit (consider transfer to nearest Cardiac Transplant Unit). Treat as above. Consider high dose methylprednisolone. Add ATG or tacrolimus if no improvement.
Neurology (Guillain-Barre Syndrome, Myesthenia, Rhabdomyolysis, Encephalitis, or Grade 3 peripheral neuropathy)	Any Grade	Permanently discontinue	Permanently discontinue
Neurology (Other)	3-4	Toxicity resolves to Grade 0-2	Toxicity does not resolve within 6 weeks of last dose or inability to reduce corticosteroid to 0.15 mg/kg (up to 10 mg) or less of prednisone or equivalent per day within 6 weeks.
Pneumonitis[d]	2	Toxicity resolves to Grade 0-1	Toxicity does not resolve within 6 weeks of last dose or inability to reduce corticosteroid to 0.15 mg/kg (up to 10 mg) or less of prednisone or equivalent per day within 6 weeks.
	3-4	Permanently discontinue	Permanently discontinue

Toxicity	Hold Treatment for Grade	Timing for Restarting Treatment	Treatment Discontinuation
Renal Failure or Nephritis	2 (if not reversible to ≤ Grade 0-1 within 7 days)	Toxicity resolves to Grade 0-1	Toxicity does not resolve within 6 weeks of last dose or inability to reduce corticosteroid to 0.15 mg/kg (up to 10 mg) or less of prednisone or equivalent per day within 6 weeks.
	3 (if not reversible to ≤ Grade 0-1 within 7 days), Grade 4	Permanently discontinue	Permanently discontinue
Skin – Rash	2	Toxicity resolves to Grade 0-1	Toxicity does not resolve within 6 weeks of last dose or inability to reduce corticosteroid to 0.15 mg/kg (up to 10 mg) or less of prednisone or equivalent per day within 6 weeks.
All Other Drug-Related Toxicity[e] (See Exception below)[f]	3 or Severe	Toxicity resolves to Grade 0-1	Toxicity does not resolve within 6 weeks of last dose or inability to reduce corticosteroid to 0.15 mg/kg (up to 10 mg) or less of prednisone or equivalent per day within 6 weeks.
	4	Permanently discontinue	Permanently discontinue

NOTE: Permanently discontinue for any severe or Grade 3 (Grade 2 for pneumonitis) drug-related AE that recurs or any life-threatening event.

[a] For patients with liver metastasis who begin treatment with Grade 2 AST or ALT, if AST or ALT increases by greater than or equal to 50% relative to baseline and lasts for at least 1 week, then patients must come off protocol therapy.

[b] The protocol distinguishes hyperglycemia responsive to insulin support from pancreatitis-associated diabetes. For the former, as long as laboratory abnormalities are addressed with appropriate supportive care, treatment may continue. For Grade 2 or higher pancreatitis-associated diabetes, patients must come off protocol therapy.

[c] If symptoms resolve within one 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 subject should be pre-medicated for the next scheduled dose.

[d] Patients will come off study drug if steroids are required to treat drug-related pulmonary toxicity, but not if transient steroids are used to treat other pathology, such as an asthma exacerbation, for example.

[e] Patients with intolerable or persistent Grade 2 drug-related AE may hold study medication at physician discretion. Permanently discontinue study drug for persistent Grade 2 adverse reactions for which treatment with study drug has been held, that do not recover to Grade 0-1 within 6 weeks of the last dose.

[f] Exception: Any Grade 3 or 4 drug-related laboratory abnormality or electrolyte abnormality, that can be managed with electrolyte replacement, hormone replacement, insulin, or that does not require treatment, does not require discontinuation of nivolumab.

5.3.1 Any Grade 2 drug-related uveitis, eye pain, or blurred vision that does not respond to topical therapy and does not improve to Grade 1 severity within the re-treatment period OR requires systemic treatment must go off protocol treatment.

5.3.2 **Infusion Reaction Management Guidelines**

Treatment recommendations are provided below and may be modified based on local treatment standards and guidelines as medically appropriate:

Remain at bedside and monitor subject until recovery from symptoms.

5.3.2.1 <u>For Grade 1 symptoms</u>: (Mild reaction; infusion interruption not indicated; intervention not indicated)

Infusion rate may be slowed or interrupted and restarted at 50% of the original infusion rate when symptoms resolve; if no further complications

ensue after 30 minutes, the rate may be increased to 100% of the original infusion rate. Monitor patient closely.

The following prophylactic premedications are recommended for future infusions: diphenhydramine (or equivalent) and/or paracetamol (acetaminophen) at least 30 minutes before additional nivolumab administrations, slowing infusion rate as above.

5.3.2.2 For Grade 2 symptoms: (Moderate reaction requires therapy or infusion interruption but responds promptly to symptomatic treatment [e.g., antihistamines, non-steroidal anti-inflammatory drugs, narcotics, corticosteroids, bronchodilators, IV fluids]; close observation for recurrence and treatment medications may need to be continued for 24-48 hours, and no further nivolumab will be administered at that visit.)

Stop the nivolumab infusion, begin an IV infusion of normal saline, and treat the subject with diphenhydramine and/or paracetamol (acetaminophen); remain at bedside and monitor patient until resolution of symptoms. Corticosteroid or bronchodilator therapy may also be administered as appropriate. If the infusion is interrupted, then restart the infusion at 50% of the original infusion rate when symptoms resolve; if no further complications ensue after 30 minutes, the rate may be increased to 100% of the original infusion rate. Monitor patient closely. If symptoms recur, re-administer diphenhydramine IV, remain at bedside, and monitor the patient until resolution of symptoms. The amount of study drug infused must be recorded on the electronic case report form (eCRF).

The following prophylactic premedications are recommended for future infusions: diphenhydramine (or equivalent) and acetaminophen (or paracetamol) should be administered at least 30 minutes before additional nivolumab administrations. If necessary, corticosteroids (recommended dose of up to 25 mg of IV hydrocortisone or equivalent) may be used.

5.3.2.3 For Grade 3 or Grade 4 symptoms: (Severe reaction)

Grade 3 symptoms: prolonged (i.e., not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for other clinical sequelae (e.g., renal impairment, pulmonary infiltrates).

Grade 4 symptoms: (life threatening; pressor or ventilatory support indicated).

Nivolumab will be permanently discontinued
Immediately discontinue infusion of nivolumab. Begin an IV infusion of normal saline, and bronchodilators, epinephrine 1:1,000 solution for subcutaneous administration or 1:10,000 solution injected slowly for IV administration, and/or diphenhydramine IV with methylprednisolone IV (or equivalent), as needed. Patient should be monitored until the investigator is comfortable that the symptoms will not recur.

Investigators should follow their institutional guidelines for the treatment of anaphylaxis. Remain at bedside and monitor patient until recovery from symptoms.

5.3.3 In the case of late-occurring hypersensitivity symptoms (e.g., appearance of a localized or generalized pruritus within 1 week after treatment), symptomatic treatment may be given (e.g., oral antihistamine, or corticosteroids). Additional treatment may be administered prior to next dose as per guidelines in Section 5.3.2.

Please note that late occurring events, including isolated fever and fatigue, may represent the presentation of systemic inflammation. Please evaluate accordingly.

5.3.4 Any adverse event, laboratory abnormality, or intercurrent illness which, in the judgment of the investigator, presents a substantial clinical risk to the subject with continued study drug dosing should go off protocol treatment.

5.3.5 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). Subjects must resume protocol therapy within 6 weeks of the scheduled interruption. Nivolumab dosing interruption lasting > 6 weeks will require treatment discontinuation, with the following exception: Dosing interruptions > 6 weeks that occur for non-drug-related reasons may be allowed. The study chair should be notified when treatment is re-initiated in a subject with a dosing interruption lasting > 6 weeks. The reason for interruption should be documented in the patient's study record. If toxicity does not resolve to Grade 0-1 within 6 weeks after last infusion, protocol therapy should be discontinued. Subjects with a laboratory adverse event still at Grade 2 after 6 weeks may continue protocol therapy only if asymptomatic and controlled.

6.0 DRUG INFORMATION

6.1 AXITINIB

(Inlyta®, AG-013736) NSC# 757441, IND# [redacted] **(05/21/20)**

Source and Pharmacology:

Axitinib is an oral selective second generation tyrosine kinase inhibitor which blocks angiogenesis and tumor growth by inhibiting vascular endothelial growth factor receptors (VEGFR-1, VEGFR-2, and VEGFR-3). VEGF receptors are critical components of the processes leading to the branching, extension, and survival of endothelial cells which form new blood vessels during angiogenesis, an absolute necessity for tumor growth beyond microscopic size. Dynamic contrast enhanced-magnetic resonance imaging (Dce-MRI) studies showed that axitinib treatment decreased the overall tumor blood flow/permeability at as early as 2 days after initiation of treatment, with a maximum reduction in permeability surface area product (Ktrans) observed on Day 7 after dosing. The change in vascular Ktrans correlated with decreased microvessel density, cellular viability, and tumor growth. Axitinib is FDA approved for the treatment of advanced renal cell carcinoma after failure of one prior systemic therapy.

Studies showed that the anti-tumor efficacy of axitinib is not driven by Cmax, rather by adequate plasma exposure above the concentration for VEGFR target inhibition (Ctarget) over a prolonged period of time. Based on a series of studies using various xenograft tumor models, the pharmacologically active axitinib concentration for Ctarget was estimated as 0.1-0.49 nM (or 0.04-0.19 ng/mL, unbound). This translates to a human Ctarget of 24-98 nM (or 9.3-38 ng/mL, total plasma concentration), assuming a 99.5% human plasma protein binding.

Axitinib is rapidly absorbed with bioavailability of 58% and maximal plasma concentrations (Cmax) generally occurring within the first 4 hours following oral administration. The plasma pharmacokinetics of axitinib at steady state are generally linear, with Cmax of 28.7-39.5 ng/mL, AUC0-24 of 261-382 ng•h /mL, mean volume of distribution (Vz/F) of 93.7-122 L, and half-life of 2.2-5.2 hours at the initial 5 mg BID dose. Axitinib is highly bound to plasma proteins (99.5%). Renal excretion does not contribute to the elimination of axitinib, which occurs primarily via hepatobiliary excretion. The estimated systemic clearance of 21 L/hr in plasma for axitinib (following administration of a 1-mg intravenous dose) is lower than hepatic blood flow (87 L/hr) in humans indicating a modest first-pass effect for axitinib. Mild hepatic impairment does not alter axitinib plasma exposures (AUC0-∞ and Cmax) compared to normal hepatic function. However, there was a ~2-fold increase in axitinib AUC0-∞ and a 1.3-fold increase in axitinib Cmax in subjects with moderate hepatic impairment.

Drug Interactions:
Metabolism of axitinib is primarily mediated by the CYP3A4 drug-metabolizing enzyme, and to a lesser extent by CYP1A2, CYP2C19, and UGT1A1 as determined from in vitro studies with human liver microsomes. Ketoconazole (a potent CYP3A4 inhibitor) increased plasma exposure of axitinib 2-fold and peak plasma concentration 1.5-fold. Rifampin (a potent CYP3A4 inducer) caused a 79% decrease in axitinib plasma exposures and a 71% decrease in axitinib peak plasma concentrations.

Axitinib is an inhibitor of CYP2C8 in vitro, however, drug interactions studies with paclitaxel (CYP2C8 substrate) demonstrated lack of in vivo inhibition of CYP2C8 by axitinib at a dose of 5 mg BID. Data from phase I/II studies indicated that plasma profiles and pharmacokinetic parameters of paclitaxel, carboplatin, capecitabine, gemcitabine, cisplatin, pemetrexed, oxaliplatin, 5-FU, bevacizumab, and irinotecan (including SN-38) were similar in the absence and presence of axitinib.

Patients should be counseled to avoid strong inhibitors and inducers of CYP3A4. Please see Appendix VI for potential drug interactions with axitinib.

Patient Considerations:
Axitinib can cause fetal harm when administered to a pregnant woman based on its mechanism of action. There are no adequate and well-controlled studies in pregnant women using this agent. In developmental toxicity studies in mice, axitinib was teratogenic, embryotoxic and fetotoxic at maternal exposures that were lower than human exposures at the recommended clinical dose. Women of childbearing potential should be advised to avoid becoming pregnant while receiving axitinib.

Mothers taking this drug should not breastfeed.

Toxicity:

Comprehensive Adverse Events and Potential Risks list (CAEPR) for Axitinib (AG-013736, NSC 757441)

The Comprehensive Adverse Events and Potential Risks list (CAEPR) provides a single list of reported and/or potential adverse events (AE) associated with an agent using a uniform presentation of events by body system. In addition to the comprehensive list, a subset, the Specific Protocol Exceptions to Expedited Reporting (SPEER), appears in a separate column and is identified with bold and italicized text. This subset of AEs (SPEER) is a list of events that are protocol specific exceptions to expedited reporting to NCI (except as noted below). Refer to the 'CTEP, NCI Guidelines: Adverse Event Reporting Requirements' http://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/aeguidelines.pdf for further clarification. *Frequency is provided based on 1659 patients.* Below is the CAEPR for Axitinib (AG-013736).

NOTE: Report AEs on the SPEER **ONLY IF** they exceed the grade noted in parentheses next to the AE in the SPEER. If this CAEPR is part of a combination protocol using multiple investigational agents and has an AE listed on different SPEERs, use the lower of the grades to determine if expedited reporting is required.

Version 2.2, March 26, 2020[1]

Adverse Events with Possible Relationship to Axitinib (AG-013736) (CTCAE 5.0 Term) [n= 1659]			**Specific Protocol Exceptions to Expedited Reporting (SPEER)**
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	
BLOOD AND LYMPHATIC SYSTEM DISORDERS			
Anemia			***Anemia (Gr 2)***
CARDIAC DISORDERS			
		Heart failure	
ENDOCRINE DISORDERS			
		Hyperthyroidism	
Hypothyroidism			***Hypothyroidism (Gr 2)***
GASTROINTESTINAL DISORDERS			
Abdominal pain			***Abdominal pain (Gr 2)***
	Constipation		***Constipation (Gr 2)***
Diarrhea			***Diarrhea (Gr 2)***
	Dyspepsia		***Dyspepsia (Gr 2)***
		Gastrointestinal fistula[2]	
		Gastrointestinal hemorrhage[3]	
		Gastrointestinal perforation[4]	
	Mucositis oral		***Mucositis oral (Gr 2)***
Nausea			***Nausea (Gr 2)***
Vomiting			***Vomiting (Gr 2)***
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS			
Fatigue			***Fatigue (Gr 2)***
INFECTIONS AND INFESTATIONS			
	Infection[5]		
INJURY, POISONING AND PROCEDURAL COMPLICATIONS			
		Wound complication	
INVESTIGATIONS			
Alanine aminotransferase increased			***Alanine aminotransferase increased (Gr 2)***
Alkaline phosphatase increased			***Alkaline phosphatase increased (Gr 2)***

Adverse Events with Possible Relationship to Axitinib (AG-013736) (CTCAE 5.0 Term) [n= 1659]			Specific Protocol Exceptions to Expedited Reporting (SPEER)
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	
Aspartate aminotransferase increased			***Aspartate aminotransferase increased (Gr 2)***
	Blood bilirubin increased		***Blood bilirubin increased (Gr 2)***
Creatinine increased			***Creatinine increased (Gr 2)***
		Hemoglobin increased	
	INR increased		
	Lipase increased		***Lipase increased (Gr 2)***
Lymphocyte count decreased			***Lymphocyte count decreased (Gr 2)***
	Neutrophil count decreased		***Neutrophil count decreased (Gr 2)***
Platelet count decreased			***Platelet count decreased (Gr 2)***
	Serum amylase increased		***Serum amylase increased (Gr 2)***
Weight loss			***Weight loss (Gr 2)***
	White blood cell decreased		***White blood cell decreased (Gr 2)***
METABOLISM AND NUTRITION DISORDERS			
Anorexia			***Anorexia (Gr 2)***
	Dehydration		
	Hypercalcemia		***Hypercalcemia (Gr 2)***
Hyperglycemia			***Hyperglycemia (Gr 2)***
Hyperkalemia			***Hyperkalemia (Gr 2)***
	Hypernatremia		
Hypoalbuminemia			***Hypoalbuminemia (Gr 2)***
	Hypocalcemia		***Hypocalcemia (Gr 2)***
	Hypoglycemia		***Hypoglycemia (Gr 2)***
	Hypokalemia		***Hypokalemia (Gr 2)***
Hyponatremia			***Hyponatremia (Gr 2)***
	Hypophosphatemia		***Hypophosphatemia (Gr 2)***
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS			
	Arthralgia		***Arthralgia (Gr 2)***
	Back pain		***Back pain (Gr 2)***
	Pain in extremity		***Pain in extremity (Gr 2)***
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS)			
	Treatment related secondary malignancy		
NERVOUS SYSTEM DISORDERS			
	Dizziness		
	Dysgeusia		
	Headache		***Headache (Gr 2)***
		Intracranial hemorrhage	
		Reversible posterior leukoencephalopathy syndrome	
RENAL AND URINARY DISORDERS			
		Hematuria	
	Proteinuria		***Proteinuria (Gr 2)***
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS			
		Bronchopulmonary hemorrhage	
	Cough		***Cough (Gr 2)***

Adverse Events with Possible Relationship to Axitinib (AG-013736) (CTCAE 5.0 Term) [n= 1659]			Specific Protocol Exceptions to Expedited Reporting (SPEER)
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	
	Dyspnea		***Dyspnea (Gr 2)***
		Epistaxis	
Voice alteration			***Voice alteration (Gr 2)***
SKIN AND SUBCUTANEOUS TISSUE DISORDERS			
Palmar-plantar erythrodysesthesia syndrome			***Palmar-plantar erythrodysesthesia syndrome (Gr 2)***
	Rash maculo-papular		***Rash maculo-papular (Gr 2)***
VASCULAR DISORDERS			
		Arterial thromboembolism	
Hypertension		Thromboembolic event	***Hypertension (Gr 2)***
		Vascular disorders - Other (aneurysms and artery dissections)	

[1]This table will be updated as the toxicity profile of the agent is revised. Updates will be distributed to all Principal Investigators at the time of revision. The current version can be obtained by contacting PIO@CTEP.NCI.NIH.GOV. Your name, the name of the investigator, the protocol and the agent should be included in the e-mail.

[2]Gastrointestinal fistula includes Anal fistula, Colonic fistula, Duodenal fistula, Esophageal fistula, Enterovesical fistula, Gastric fistula, Gastrointestinal fistula, Ileal fistula, Jejunal fistula, Oral cavity fistula, Pancreatic fistula, Rectal fistula, and Salivary gland fistula under the GASTROINTESTINAL DISORDERS SOC.

[3]Gastrointestinal hemorrhage includes Anal hemorrhage, Cecal hemorrhage, Colonic hemorrhage, Duodenal hemorrhage, Esophageal hemorrhage, Esophageal varices hemorrhage, Gastric hemorrhage, Hemorrhoidal hemorrhage, Ileal hemorrhage, Intra-abdominal hemorrhage, Jejunal hemorrhage, Lower gastrointestinal hemorrhage, Oral hemorrhage, Pancreatic hemorrhage, Rectal hemorrhage, Retroperitoneal hemorrhage, and Upper gastrointestinal hemorrhage under the GASTROINTESTINAL DISORDERS SOC.

[4]Gastrointestinal perforation includes Colonic perforation, Duodenal perforation, Esophageal perforation, Gastric perforation, Ileal perforation, Jejunal perforation, Rectal perforation, and Small intestinal perforation under the GASTROINTESTINAL DISORDERS SOC.

[5]Infection includes all 75 sites of infection under the INFECTIONS AND INFESTATIONS SOC.

Adverse events reported on axitinib (AG-013736) trials, but for which there is insufficient evidence to suggest that there was a reasonable possibility that axitinib (AG-013736) caused the adverse event:

BLOOD AND LYMPHATIC SYSTEM disorders - Blood and lymphatic system disorders - Other (polycythemia); Febrile neutropenia
CARDIAC DISORDERS - Atrial fibrillation; Atrial flutter; Cardiac arrest; Cardiac disorders - Other (left ventricular dysfunction); Chest pain - cardiac; Myocardial infarction; Pericardial effusion; Pericarditis; Right ventricular dysfunction; Sinus bradycardia; Sinus tachycardia; Supraventricular tachycardia
EAR AND LABYRINTH DISORDERS - Tinnitus
EYE DISORDERS - Blurred vision; Cataract; Eye disorders - Other (blindness); Retinal vascular disorder
GASTROINTESTINAL DISORDERS - Abdominal distension; Ascites; Colitis; Dry mouth; Duodenal ulcer; Dysphagia; Enterocolitis; Esophagitis; Gastric ulcer; Gastritis; Gastroesophageal reflux disease; Gastrointestinal disorders - Other (diverticulitis); Gastrointestinal disorders - Other (gastroenteritis); Gastrointestinal disorders - Other (inguinal hernia); Ileus; Oral pain; Pancreatitis; Small intestinal obstruction; Stomach pain

GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS - Chills; Edema limbs; Fever; Malaise; Multi-organ failure; Non-cardiac chest pain; Pain
HEPATOBILIARY DISORDERS - Bile duct stenosis; Cholecystitis; Gallbladder necrosis; Gallbladder obstruction; Hepatic failure; Hepatobiliary disorders - Other (bile duct stone); Hepatobiliary disorders - Other (cholestasis); Hepatobiliary disorders - Other (colelithiasis); Hepatobiliary disorders - Other (hepatorenal syndrome); Hepatobiliary disorders - Other (jaundice)
IMMUNE SYSTEM DISORDERS - Allergic reaction
INJURY, POISONING AND PROCEDURAL COMPLICATIONS - Fall; Fracture; Spinal fracture
INVESTIGATIONS - GGT increased
METABOLISM AND NUTRITION DISORDERS - Hypermagnesemia; Hypomagnesemia; Metabolism and nutrition disorders - Other (cachexia)
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS - Flank pain; Generalized muscle weakness; Myalgia; Neck pain; Trismus
NERVOUS SYSTEM DISORDERS - Dysphasia; Encephalopathy; Ischemia cerebrovascular; Lethargy; Paresthesia; Peripheral sensory neuropathy; Presyncope; Seizure; Somnolence; Stroke; Syncope; Transient ischemic attacks
PSYCHIATRIC DISORDERS - Anxiety; Confusion; Depression; Insomnia; Psychiatric disorders - Other (mental status changes)
RENAL AND URINARY DISORDERS - Acute kidney injury; Dysuria; Renal and urinary disorders - Other (acute prerenal failure); Urinary retention; Urinary tract obstruction
REPRODUCTIVE SYSTEM AND BREAST DISORDERS - Vaginal pain
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS - Atelectasis; Hoarseness; Hypoxia; Oropharyngeal pain; Pleural effusion; Pneumonitis; Pneumothorax; Pulmonary edema; Respiratory failure; Respiratory, thoracic and mediastinal disorders - Other (chronic obstructive pulmonary disease); Sore throat
SKIN AND SUBCUTANEOUS TISSUE DISORDERS - Alopecia; Dry skin; Hyperhidrosis; Pain of skin; Pruritus; Rash acneiform; Skin and subcutaneous tissue disorders - Other (scrotal skin rash); Skin ulceration
VASCULAR DISORDERS - Hypotension; Vascular disorders - Other (circulatory collapse)

Note: Axitinib (AG-013736) in combination with other agents could cause an exacerbation of any adverse event currently known to be caused by the other agent, or the combination may result in events never previously associated with either agent.

Formulation and Stability:

Formulation

The agent is supplied as 1 mg and 5 mg tablets for oral administration. The 1 mg tablets are red film-coated, oval tablets debossed with “Pfizer” on one side and “1 XNB” on the other; available in bottles of 180 tablets each. The 5 mg tablets are red film-coated, triangular tablets debossed with “Pfizer” on one side and “5 XNB” on the other; available in bottles of 60 tablets each. Tablet excipients include microcrystalline cellulose, lactose monohydrate, croscarmellose sodium, and magnesium stearate. The Opadry II red 32K15441 film coating contains lactose monohydrate, HPMC 2910/Hypromellose 15cP, titanium dioxide, triacetin (glycerol triacetate), and red iron oxide.

Stability and Storage

Store at 20 °C to 25 °C (68 °F to 77 °F); excursions permitted to 15 °C to 30 °C (59 °F to 86 °F) [USP Controlled Room Temperature]. Refer to the package label for expiration. If a storage temperature excursion is identified, promptly return axitinib to controlled room temperature and quarantine the supplies. Provide a detailed report of the excursion (including documentation of temperature monitoring and duration of the excursion) to PMBAfterHours@mail.nih.gov for determination of suitability.

Tablets may be removed from the original container and repackaged in a vial suitable for oral tablets by the dispensing pharmacy.

Guidelines for Administration:
See Treatment Details (Section 4.0) and Dose Modifications (Section 5.0) of the protocol.

Axitinib should be taken by mouth twice daily approximately 12 hours apart. Axitinib may be taken with or without food. Tablets should be administered whole and intact with a glass of water or other liquid; do not crush or cut tablets. If a dose is missed or vomited, the patient/subject should not try to repeat or "catch up" the dose. The next dose should be given at the next regularly scheduled time point.

Supplier:
Axitinib is supplied by Pfizer Inc. and distributed by the CTEP, Division of Cancer Treatment and Diagnosis (DCTD), NCI. **Do not use commercial supply.**

Obtaining the Agent
Agent Ordering
NCI supplied agent may be requested by the eligible participating investigator (or their authorized designee) at each participating institution. The CTEP assigned protocol number must be used for ordering all CTEP supplied investigational agents. The responsible investigator at each participating institution must be registered with CTEP, DCTD through an annual submission of FDA form 1572 (Statement of Investigator), NCI Biosketch, Agent Shipment Form, and Financial Disclosure Form (FDF). If there are several participating investigators at one institution, CTEP supplied investigational agents for the study should be ordered under the name of one lead participating investigator at that institution.

Sites may order initial agent supplies when a subject has been randomized.

Submit agent requests through the PMB Online Agent Order Processing (OAOP) application. Access to OAOP requires the establishment of a CTEP Identity and Access Management (IAM) account and the maintenance of an "active" account status, and a "current" password, and active person registration status. For questions about drug orders, transfers, returns, or accountability, call or email PMB any time. Refer to the PMB's website for specific policies and guidelines related to agent management.

Agent Accountability
Agent Inventory Records
The investigator, or a responsible party designated by the investigator, must maintain a careful record of the receipt, dispensing and final disposition of all agents received from the PMB using the appropriate NCI Investigational Agent (Drug) Accountability Record (DARF) available on the CTEP forms page. Store and maintain separate NCI Investigational Agent Accountability Records for each agent, strength, formulation and ordering investigator on this protocol.

Investigator Brochure Availability
The current version(s) of the IB(s) for the agent will be accessible to site investigators and research staff through the PMB Online Agent Order Processing (OAOP) application. Access to OAOP requires the establishment of a CTEP IAM account and the maintenance

of an "active" account status, a "current" password, and active person registration status. Questions about IB access may be directed to the PMB IB coordinator via email.

Useful Links and Contacts

- CTEP Forms, Templates, Documents: http://ctep.cancer.gov/forms/
- NCI CTEP Investigator Registration: RCRHelpDesk@nih.gov
- PMB policies and guidelines: http://ctep.cancer.gov/branches/pmb/agent_management.htm
- PMB Online Agent Order Processing (OAOP) application: https://ctepcore.nci.nih.gov/OAOP/
- CTEP Identity and Access Management (IAM) account: https://ctepcore.nci.nih.gov/iam/
- CTEP IAM account help: ctepreghelp@ctep.nci.nih.gov
- PMB email: PMBAfterHours@mail.nih.gov
- IB Coordinator: IBCoordinator@mail.nih.gov
  PMB phone and hours of service: (240) 276-6575 Monday through Friday between 8:30 am and 4:30 pm (ET)

6.2 NIVOLUMAB

(BMS-936558, MDX1106, ONO-4538, anti-PD-1, Opdivo®) NSC# 748726, IND# [redacted] **(03/09/2021)**

Source and Pharmacology:

Nivolumab is a fully human immunoglobulin G4 (IgG4) monoclonal antibody that selectively inhibits programmed cell death-1 (PD-1) activity by binding to the PD-1 receptor to block the ligands PD-L1 and PD-L2 from binding. The negative PD-1 receptor signaling that regulates T-cell activation and proliferation is therefore disrupted. This releases PD-1 pathway-mediated inhibition of the immune response, including the antitumor immune response. The clinical activity of nivolumab was initially evaluated in malignant melanoma and squamous non−small cell lung cancer (NSCLC), and the remarkable response rates, prolonged survival, and better safety profile were the basis of regulatory approval. Nivolumab is FDA-approved for a variety of solid tumors including advanced renal cell carcinoma (RCC).

The pharmacokinetics of single-agent nivolumab was studied in patients over a dose range of 0.1 to 20 mg/kg administered as a single dose or as multiple doses every 2 or 3 weeks. Nivolumab clearance decreases over time, resulting in a geometric mean steady state clearance (CLss) of 8.2 mL/h; the decrease in CLss is not considered clinically relevant. The geometric mean volume of distribution at steady state (Vss) is 6.8 L, and geometric mean elimination half-life is 25 days. Steady-state concentrations of nivolumab were reached by approximately 12 weeks when administered at 3 mg/kg every 2 weeks, and systemic accumulation was approximately 3.7-fold. The exposure to nivolumab increased dose proportionally over the dose range of 0.1 to 10 mg/kg administered every 2 weeks.

No formal pharmacokinetic drug-drug interaction studies have been conducted with nivolumab. The indirect drug-drug interaction potential of nivolumab was assessed using systemic cytokine modulation data for cytokines known to modulate CYP enzymes. There were no meaningful changes in cytokines known to have indirect effects on CYP enzymes across all dose levels of nivolumab. This lack of cytokine modulation suggests that

nivolumab has no or low potential for modulating CYP enzymes, thereby indicating a low risk of therapeutic protein-drug interaction.

Patient Care Implications
Adverse events were observed in animal reproduction studies. Nivolumab may be expected to cross the placenta; effects to the fetus may be greater in the second and third trimesters. Based on its mechanism of action, nivolumab is expected to cause fetal harm if used during pregnancy. Women of childbearing potential (WOCBP) receiving nivolumab must continue contraception for a period of 5 months after the last dose of nivolumab. Men receiving nivolumab and who are sexually active with WOCBP must continue contraception for a period of 7 months after the last dose of nivolumab.

It is not known if nivolumab is present in breast milk. Due to the potential for serious adverse reactions in the breastfed infant, the manufacturer recommends to discontinue breastfeeding during treatment.

Toxicity:

Comprehensive Adverse Events and Potential Risks list (CAEPR)
for
(Nivolumab NSC 748726)

The Comprehensive Adverse Events and Potential Risks list (CAEPR) provides a single list of reported and/or potential adverse events (AE) associated with an agent using a uniform presentation of events by body system. In addition to the comprehensive list, a subset, the Specific Protocol Exceptions to Expedited Reporting (SPEER), appears in a separate column and is identified with bold and italicized text. This subset of AEs (SPEER) is a list of events that are protocol specific exceptions to expedited reporting to NCI (except as noted below). Refer to the 'CTEP, NCI Guidelines: Adverse Event Reporting Requirements' http://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/aeguidelines.pdf for further clarification. *Frequency is provided based on 2069 patients.* Below is the CAEPR for Nivolumab.

NOTE: Report AEs on the SPEER **ONLY IF** they exceed the grade noted in parentheses next to the AE in the SPEER. If this CAEPR is part of a combination protocol using multiple investigational agents and has an AE listed on different SPEERs, use the lower of the grades to determine if expedited reporting is required.

Version 2.4, December 2, 2020[1]

Adverse Events with Possible Relationship to Nivolumab (CTCAE 5.0 Term) [n= 2069]			**Specific Protocol Exceptions to Expedited Reporting (SPEER)**
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	
BLOOD AND LYMPHATIC SYSTEM DISORDERS			
	Anemia		***Anemia (Gr 3)***
CARDIAC DISORDERS			
		Cardiac disorders - Other (cardiomyopathy)	
		Myocarditis	
		Pericardial tamponade[2]	
		Pericarditis	
ENDOCRINE DISORDERS			

Adverse Events with Possible Relationship to Nivolumab (CTCAE 5.0 Term) [n= 2069]			Specific Protocol Exceptions to Expedited Reporting (SPEER)
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	
	Adrenal insufficiency[3]		
	Hyperthyroidism[3]		
	Hypophysitis[3]		
	Hypothyroidism[3]		
EYE DISORDERS			
		Blurred vision	
		Dry eye	
		Eye disorders - Other (diplopia) [3]	
		Eye disorders - Other (Graves ophthalmopathy) [3]	
		Eye disorders - Other (optic neuritis retrobulbar) [3]	
		Eye disorders - Other (Vogt-Koyanagi-Harada)	
	Uveitis		
GASTROINTESTINAL DISORDERS			
	Abdominal pain		***Abdominal pain (Gr 2)***
	Colitis[3]		
		Colonic perforation[3]	
	Diarrhea Dry mouth		***Diarrhea (Gr 3)*** ***Dry mouth (Gr 2)***
		Enterocolitis	
		Gastritis	
		Mucositis oral	
	Nausea		***Nausea (Gr 2)***
	Pancreatitis[4]		
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS			
Fatigue			***Fatigue (Gr 3)***
	Fever		***Fever (Gr 2)***
	Injection site reaction		***Injection site reaction (Gr 2)***
HEPATOBILIARY DISORDERS			
		Hepatobiliary disorders - Other (immune-mediated hepatitis)	
IMMUNE SYSTEM DISORDERS			
		Allergic reaction[3]	
		Autoimmune disorder[3]	
		Cytokine release syndrome[5]	
		Immune system disorders - Other (GVHD in the setting of allotransplant) [3,6]	
		Immune system disorders - Other (sarcoidosis) [3]	
INJURY, POISONING AND PROCEDURAL COMPLICATIONS			
	Infusion related reaction[7]		
INVESTIGATIONS			
	Alanine aminotransferase increased[3]		***Alanine aminotransferase increased[3] (Gr 3)***

Adverse Events with Possible Relationship to Nivolumab (CTCAE 5.0 Term) [n= 2069]			Specific Protocol Exceptions to Expedited Reporting (SPEER)
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	
	Aspartate aminotransferase increased[3]		***Aspartate aminotransferase increased[3](Gr 3)***
	Blood bilirubin increased[3]		***Blood bilirubin increased[3](Gr 2)***
	CD4 lymphocytes decreased		***CD4 lymphocyte decreased (Gr 4)***
	Creatinine increased		
	Lipase increased		
	Lymphocyte count decreased		***Lymphocyte count decreased (Gr 4)***
	Neutrophil count decreased		
	Platelet count decreased		
	Serum amylase increased		
METABOLISM AND NUTRITION DISORDERS			
	Anorexia		
		Hyperglycemia	***Hyperglycemia (Gr 2)***
		Metabolism and nutrition disorders - Other (diabetes mellitus with ketoacidosis)[3]	
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS			
	Arthralgia		
		Musculoskeletal and connective tissue disorder - Other (polymyositis)	
		Myositis	
		Rhabdomyolysis	
NERVOUS SYSTEM DISORDERS			
		Encephalopathy[3]	
		Facial nerve disorder[3]	
		Guillain-Barre syndrome[3]	
		Myasthenia gravis[3]	
		Nervous system disorders - Other (demyelination myasthenic syndrome)	
		Nervous system disorders - Other (encephalitis)[3]	
		Nervous system disorders - Other (meningoencephalitis)	
		Nervous system disorders - Other (meningoradiculitis)[3]	
		Nervous system disorders - Other (myasthenic syndrome)	
		Peripheral motor neuropathy	
		Peripheral sensory neuropathy	
		Reversible posterior leukoencephalopathy syndrome3	
RENAL AND URINARY DISORDERS			
		Acute kidney injury[3]	
		Renal and urinary disorders - Other (immune-mediated nephritis)	
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS			

Adverse Events with Possible Relationship to Nivolumab (CTCAE 5.0 Term) [n= 2069]			Specific Protocol Exceptions to Expedited Reporting (SPEER)
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	
	Pleural effusion[3]		
	Pneumonitis[3]		
		Respiratory, thoracic and mediastinal disorders - Other (bronchiolitis obliterans with organizing pneumonia)[3]	
SKIN AND SUBCUTANEOUS TISSUE DISORDERS			
		Erythema multiforme[3]	
	Pruritus[3]		***Pruritus[3] (Gr 2)***
	Rash maculo-papular[3]		***Rash maculo-papular[3] (Gr 2)***
		Skin and subcutaneous tissue disorders - Other (bullous pemphigoid)	
	Skin and subcutaneous tissue disorders - Other (Sweet's Syndrome)[3]		
	Skin hypopigmentation[3]		
		Stevens-Johnson syndrome	
		Toxic epidermal necrolysis	

[1]This table will be updated as the toxicity profile of the agent is revised. Updates will be distributed to all Principal Investigators at the time of revision. The current version can be obtained by contacting PIO@CTEP.NCI.NIH.GOV. Your name, the name of the investigator, the protocol and the agent should be included in the e-mail.

[2]Pericardial tamponade may be related to possible inflammatory reaction at tumor site.

[3] Nivolumab being a member of class of agents involved in the inhibition of "immune checkpoints", may result in severe and possibly fatal immune-mediated adverse events probably due to T-cell activation and proliferation. This may result in autoimmune disorders that can include (but are not limited to) autoimmune hemolytic anemia, acquired anti-factor VIII immune response, autoimmune aseptic meningitis, autoimmune hepatitis, autoimmune nephritis, autoimmune neuropathy, autoimmune thyroiditis, bullous pemphigoid, exacerbation of Churg-Strauss Syndrome, drug rash with eosinophilia systemic symptoms [DRESS] syndrome, facial nerve disorder (facial nerve paralysis), limbic encephalitis, hepatic failure, pure red cell aplasia, pancreatitis, ulcerative and hemorrhagic colitis, endocrine disorders (e.g., autoimmune thyroiditis, hyperthyroidism, hypothyroidism, autoimmune hypophysitis/hypopituitarism, thyrotoxicosis, and adrenal insufficiency), sarcoid granuloma, myasthenia gravis, polymyositis, and Guillain-Barre syndrome.

[4]Pancreatitis may result in increased serum amylase and/or more frequently lipase.

[5]Cytokine release syndrome may manifest as hemophagocytic lymphohistiocytosis with accompanying fever and pancytopenia.

[6]Complications including hyperacute graft-versus-host disease (GVHD), some fatal, have occurred in patients receiving allo stem cell transplant (SCT) after receiving Nivolumab. These complications may occur despite intervening therapy between receiving Nivolumab and allo-SCT.

[7]Infusion reactions, including high-grade hypersensitivity reactions which have been observed following administration of nivolumab, may manifest as fever, chills, shakes, itching, rash, hypertension or hypotension, or difficulty breathing during and immediately after administration of nivolumab.

Adverse events reported on Nivolumab trials, but for which there is insufficient evidence to suggest that there was a reasonable possibility that Nivolumab caused the adverse event:

BLOOD AND LYMPHATIC SYSTEM DISORDERS - Leukocytosis
CARDIAC DISORDERS - Atrial fibrillation; Atrioventricular block complete; Heart failure; Ventricular arrhythmia
EAR AND LABYRINTH DISORDERS - Vestibular disorder
EYE DISORDERS - Eye disorders - Other (iridocyclitis); Optic nerve disorder; Periorbital edema
GASTROINTESTINAL DISORDERS - Constipation; Duodenal ulcer; Flatulence; Gastrointestinal disorders - Other (mouth sores); Vomiting
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS - Chills; Edema limbs; Malaise; Pain
HEPATOBILIARY DISORDERS - Bile duct stenosis
IMMUNE SYSTEM DISORDERS - Anaphylaxis; Immune system disorders - Other (autoimmune thrombotic microangiopathy); Immune system disorders - Other (limbic encephalitis)
INFECTIONS AND INFESTATIONS - Bronchial infection; Lung infection; Sepsis; Upper respiratory infection
INVESTIGATIONS - Blood lactate dehydrogenase increased; GGT increased; Investigations - Other (protein total decreased); Lymphocyte count increased; Weight loss
METABOLISM AND NUTRITION DISORDERS - Dehydration; Hyperuricemia; Hypoalbuminemia; Hypocalcemia; Hyponatremia; Hypophosphatemia
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS - Back pain; Musculoskeletal and connective tissue disorder - Other (musculoskeletal pain); Musculoskeletal and connective tissue disorder - Other (polymyalgia rheumatica); Myalgia; Pain in extremity
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS) - Neoplasms benign, malignant and unspecified (incl cysts and polyps) - Other (Histiocytic necrotizing lymphadenitis)
NERVOUS SYSTEM DISORDERS - Dizziness; Headache; Intracranial hemorrhage
PSYCHIATRIC DISORDERS - Insomnia
RENAL AND URINARY DISORDERS - Hematuria; Renal and urinary disorders - Other (tubulointerstitial nephritis)
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS - Bronchospasm; Cough; Dyspnea; Hypoxia
SKIN AND SUBCUTANEOUS TISSUE DISORDERS - Alopecia; Dry skin; Hyperhidrosis; Pain of skin; Photosensitivity; Rash acneiform; Skin and subcutaneous tissue disorders - Other (rosacea)
VASCULAR DISORDERS - Flushing; Hypertension; Hypotension; Vasculitis

Note: Nivolumab in combination with other agents could cause an exacerbation of any adverse event currently known to be caused by the other agent, or the combination may result in events never previously associated with either agent.

Formulation and Stability:
The agent is a clear to opalescent, colorless to pale yellow liquid; light (few) particulates may be present. It is available in a 100 mg/10 mL vial containing a sterile, non-pyrogenic, single-use, isotonic aqueous solution formulated at 10 mg/mL in sodium citrate dihydrate, sodium chloride, mannitol, diethylenetriamine pentacetic acid (pentetic acid), polysorbate 80 (Tween® 80), and water for injection. Dilute solution of hydrochloric acid and/or sodium hydroxide may be used for pH adjustment (pH 5.5-6.5). A small amount of overfill (0.7 mL) is included with each vial to account for VNS (vial, needle, syringe) loss. The 10 mL type I flint glass vials are stoppered with fluoropolymer film-laminated rubber stoppers and sealed with aluminum seals.

Preparation: Nivolumab injection can be infused undiluted (10 mg/mL) or diluted with 0.9% Sodium Chloride Injection, USP or 5% Dextrose. When the dose is based on patient weight (i.e., mg/kg), nivolumab injection can be infused undiluted or diluted to protein concentrations as low as 0.35 mg/mL. When the dose is fixed (e.g., 240 mg or 480 mg flat dose), nivolumab injection can be infused undiluted or diluted so as not to exceed a total

infusion volume of 160 mL. For patients weighing less than 40 kilograms (kg), the total volume of infusion must not exceed 4 mL per kg of patient weight. During drug product preparation and handling, vigorous mixing or shaking is to be avoided.

Nivolumab infusions are compatible with polyvinyl chloride (PVC) or polyolefin containers and infusion sets, and glass bottles.

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

If a storage temperature excursion is identified, promptly return Nivolumab to 2°C-8°C and quarantine the supplies. Provide a detailed report of the excursion (including documentation of temperature monitoring and duration of the excursion) to PMBAfterHours@mail.nih.gov for determination of suitability.

Stability: Shelf-life surveillance of the intact vials is ongoing.

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 for nivolumab injection in IV bag includes the product administration period.

> CAUTION: The single-use vials of nivolumab for injection do not contain antibacterial preservatives or bacteriostatic agents and should be prepared as soon as possible prior to administration using aseptic technique. It is advised that the product be discarded 8 hours after initial entry.

Guidelines for Administration:
See Treatment and Dose Modification sections of the protocol.
Nivolumab is administered as an intravenous infusion over 30 minutes or per institutional guidelines through a line with a sterile 0.2 to 1.2 micron pore size, low-protein binding (polyethersulfone membrane) in-line filter. Nivolumab is not to be administered as an IV push or bolus injection. Do not administer other medications through the same IV line. Flush IV line at the end of the infusion.

Nivolumab infusions are compatible with polyvinyl chloride (PVC) or polyolefin containers and infusion sets, and glass bottles.

Supplier:
Nivolumab is supplied by Bristol-Myers-Squibb (BMS) and distributed by the Division of Cancer Treatment and Diagnosis (DCTD), NCI. **Do not use commercial supply.**

Obtaining the Agent
Agent Ordering
NCI supplied agent may be requested by the eligible participating investigator (or their authorized designee) at each participating institution. The CTEP assigned protocol number must be used for ordering all CTEP supplied investigational agents. The responsible

investigator at each participating institution must be registered with CTEP, DCTD through an annual submission of FDA form 1572 (Statement of Investigator), NCI Biosketch, Agent Shipment Form, and Financial Disclosure Form (FDF). If there are several participating investigators at one institution, CTEP supplied investigational agents for the study should be ordered under the name of one lead participating investigator at that institution.

Sites may order initial agent supplies when a subject has been randomized.

Submit agent requests through the PMB Online Agent Order Processing (OAOP) application. Access to OAOP requires the establishment of a CTEP Identity and Access Management (IAM) account and the maintenance of an "active" account status, and a "current" password, and active person registration status. For questions about drug orders, transfers, returns, or accountability, call or email PMB any time. Refer to the PMB's website for specific policies and guidelines related to agent management.

Agent Accountability

Agent Inventory Records

The investigator, or a responsible party designated by the investigator, must maintain a careful record of the receipt, dispensing and final disposition of all agents received from the PMB using the appropriate NCI Investigational Agent (Drug) Accountability Record (DARF) available on the CTEP forms page. Store and maintain separate NCI Investigational Agent Accountability Records for each agent, strength, formulation and ordering investigator on this protocol.

Investigator Brochure Availability

The current version(s) of the IB(s) for the agent will be accessible to site investigators and research staff through the PMB Online Agent Order Processing (OAOP) application. Access to OAOP requires the establishment of a CTEP IAM account and the maintenance of an "active" account status, a "current" password, and active person registration status. Questions about IB access may be directed to the PMB IB coordinator via email.

Useful Links and Contacts

- CTEP Forms, Templates, Documents: http://ctep.cancer.gov/forms/
- NCI CTEP Investigator Registration: RCRHelpDesk@nih.gov
- PMB policies and guidelines: http://ctep.cancer.gov/branches/pmb/agent_management.htm
- PMB Online Agent Order Processing (OAOP) application: https://ctepcore.nci.nih.gov/OAOP/
- CTEP Identity and Access Management (IAM) account: https://ctepcore.nci.nih.gov/iam/
- CTEP IAM account help: ctepreghelp@ctep.nci.nih.gov
- PMB email: PMBAfterHours@mail.nih.gov
- IB Coordinator: IBCoordinator@mail.nih.gov
  PMB phone and hours of service: (240) 276-6575 Monday through Friday between 8:30 am and 4:30 pm (ET)

7.0 EVALUATIONS/MATERIAL AND DATA TO BE ACCESSIONED

Timing of protocol therapy administration, response assessment studies, and surgical interventions are based on schedules derived from the experimental design or on established standards of care. Minor unavoidable departures (up to 72 hours) from protocol directed therapy and/or disease evaluations (and up to 1 week for surgery) for valid clinical, patient and family logistical, or facility, procedure and/or anesthesia scheduling issues are acceptable (except where explicitly prohibited within the protocol).

7.1 End of Therapy & Follow-up

See COG Late Effects Guidelines for recommended post treatment follow-up: http://www.survivorshipguidelines.org/.

NOTE: Follow-up data are expected to be submitted per the Case Report Forms (CRFs) schedule.

STUDIES TO BE OBTAINED	End of Therapy	At Relapse
Physical Exam	X	
Ht, Wt	X	
Performance Status	X	
CBC, differential, platelets	X	
Electrolytes including Ca^{++}, PO_4, Mg^{++}	X	
AST, ALT, albumin	X	
TSH	X	
Urinalysis	X	
Urine Protein/Creatinine	X	
ECG	X	
MUGA or ECHO	X	
Creatinine, bilirubin	X	
GFR or Creatinine Clearance	X	
Tumor Imaging	X	X
Immune Biomarkers in Blood (for consenting patients; see Section 15.2.1)	X	
Immune Biomarkers in Tissue (for consenting patients; see Section 15.2.2)		X*
Specimens for Banking (for consenting patients; see Section 15.2.3)		X*

* if available

7.2 Follow-up Studies to be Obtained

Patients must have follow-up assessments after completion of protocol therapy for a minimum of 4 years. Follow-up at year 5 and beyond is at the discretion of the treating physician.

History/Physical Exam, CBC (if clinically indicated), Electrolytes, creatinine, tumor imaging, and other studies as required for good patient care.

- Year 1 (Months 3, 6, 9, 12)

- Year 2 (Months 16, 20 and 24)
- Year 3 (Months 30 and 36)
- Year 4 (Months 42 and 48)

7.3 Research Studies for which Patient Participation is Optional

1. Immune biomarkers in blood (see Section 15.2.1) will be collected at:
   - Baseline, Day 1 of Cycles 2, 3, and 9 (within 72 hours prior to Day 1 dosing), and within 3 weeks after the last dose of study treatment.
2. Immune biomarkers in tumor tissue (see Section 15.2.2) will be collected at:
   - Baseline (if available), and at any time tumor tissue is obtained (i.e., surgery, relapse).
3. Specimens for Banking (see Section 15.2.3) will be collected at:
   - Baseline (if available), and at any time tumor tissue is obtained (i.e., surgery, relapse) for tumor tissue. Prior to any chemotherapy for whole blood, serum and urine specimens.

8.0 CRITERIA FOR REMOVAL FROM PROTOCOL THERAPY AND OFF STUDY CRITERIA

8.1 Criteria for Removal from Protocol Therapy

a) For Arms A and C, progressive disease of ≥ 40% increase in total tumor burden from baseline or nadir at any time during protocol therapy (see Section 10.2) (see exception below).
b) For Arms A and C, progressive disease of ≥ 20% increase in total tumor burden from baseline or nadir that occurs > 12 weeks after start of protocol therapy, except if a patient met the criteria for pseudoprogression in the first 12 weeks and the total tumor burden has subsequently stabilized or decreased with no additional growth (see Section 10.2) (see exception below).
c) For Arm B, progressive disease of ≥ 20% increase from baseline or nadir in total tumor burden at any time during protocol therapy (see Section 10.2).
d) Response followed by ≥ 20% increase in total tumor burden from the nadir at any time during protocol therapy (see Section 10.2.5.1) (see exception below).
e) Appearance of one or more new lesions or unequivocal progression of non-target lesions (see Section 10.2.5.2) and refer to Section 10.2.1 for exceptions within the first 12 weeks of therapy (see exception below).
f) Resection of any malignant lesion within the first 12 weeks of protocol therapy (see Section 13.1.8.1).
g) Resection of any lesion that is increasing in size at any time while on protocol therapy (see Section 13.1.8.2).
h) Completion of planned therapy.
i) Unacceptable toxicity due to protocol therapy (see Section 5.0).
j) Refusal of further protocol therapy by patient/parent/guardian.
k) Physician determines it is in patient's best interest.
l) Development of a second malignancy.
m) Pregnancy.
n) Repeat eligibility studies (if required) are outside the parameters required for eligibility (see Section 3.2).

Exception: Patients on Arm C who meet the protocol defined criteria of disease progression prior to Cycle 22 of therapy, may cross-over and receive the remainder of their protocol therapy per Arm A. For those patients who cross-over, the total protocol therapy received on AREN1721 is not to exceed 26 cycles or 2 years, whichever comes first.

Important Note: ***For criteria (a)-(c) above, calculations of percentage change in total tumor burden should fully exclude from consideration any malignant lesions that were surgically resected at any time prior to the most recent response assessment. See Section 10.2 for details.***

Patients who are off protocol therapy are to be followed until they meet the criteria for Off Study (see below). Follow-up data will be required unless patient is taken off study.

8.2 Off Study Criteria

a) Death.
b) Lost to follow-up.
c) Patient enrollment onto another COG study with tumor therapeutic intent (e.g., at recurrence).
d) Withdrawal of consent for any further data submission.
e) The fifth anniversary of the date the patient was enrolled on this study.

9.0 STATISTICAL CONSIDERATIONS

9.1 Sample Size and Study Duration

As of Amendment 5A, which now allows crossover upon progression from the nivolimab arm to the nivolumab + axitinib arm, we expect enrollment of approximately 2 patients per month. This is derived from tRCC prevalence, access to treatment centers, and enrollment patterns to date, which should be aided by the crossover.

To reduce the overall sample size from the prior design, we have maintained the same overall study design but changed two design parameters: 1-sided alpha will be increased from 0.05 to 0.15, and the targeted hazard ratio will be reduced from HR = 0.50 to HR = 0.40. With these changes, 22 PFS events will be required to address the primary objective comparing Arms A and C at the time of final analysis (see Section 9.2). Allowing that approximately 25% of eligible and evaluable patients may not have experienced a PFS event by the time of the final analysis, the target accrual on this study is 28 patients. To account for an additional estimated 5% of patients who might be found to be ineligible for the study or inevaluable for the primary endpoint at the time of or following study enrollment (e.g., due to randomization to Arm B, no central path review performed, or having central path review confirming a diagnosis other than tRCC), the ceiling accrual will be set to 40 patients, including those patients already enrolled.

If the study accrues to the target accrual without interim stopping for futility, the additional time required to enroll up to this maximum once re-opening under Amendment 5A is estimated to be 14 months. As before, all eligible patients will be followed for 5 years after randomization, and the final analysis will be conducted once the target number of PFS events needed for the final analysis has been reached, or after 2 years of follow-up is obtained for the last patient enrolled, whichever occurs first.

9.2 Study Design

With Amendment 5A, as before, eligible tRCC patients will be randomized to receive either axitinib and nivolumab (Arm A) or nivolumab alone (Arm C) in a 1:1 ratio. The enrolling institutions will assess the initial patient eligibility, including the type of RCC. Randomization will incorporate stratification for age (< 18 years vs. ≥ 18 years), and prior systemic therapy for RCC (none, anti-VEGF based therapy, or systemic therapy other than anti-VEGF). Patients may receive their assigned therapy for up to 2 years or 26 cycles of therapy, whichever occurs first, as long as they do not experience either progressive disease as defined by the immune RECIST criteria (see Section 10.2.5) or unacceptable toxicities. The primary endpoint of this study is progression-free survival (PFS), defined as the time from randomization to the earliest of disease progression (according to RECIST adapted for immunotherapy) or death due to any cause (see Sections 9.4 and 10.2).

In planning the amended 2-arm design of this study, patient-level data on tRCC patients with metastatic disease who would have been eligible for AREN1721 were extracted from three separate cohorts: 7 patients from the cohort described by Ambalavanan and Geller, 15 patients from the cohort described by Malouf et al, and 3 patients from the COG study AREN03B2.[34,24] PFS for the 3 cohorts was plotted together and found to be in agreement (log-rank test p = 0.72; Figure 1A). As such, these data were pooled into a single "historical" cohort used to select an appropriate parametric distribution for PFS in this disease setting from the proportional hazards family of models, from which determinations of power and sample size could be based. Upon superimposing the "best-fit" exponential, Weibull, and piecewise exponential models onto the Kaplan-Meier plot for PFS in the pooled historical cohort, it was determined that the piecewise exponential model offered a practically superior fit warranting the relative increase in model complexity (Figure 1B):

Figure 1A

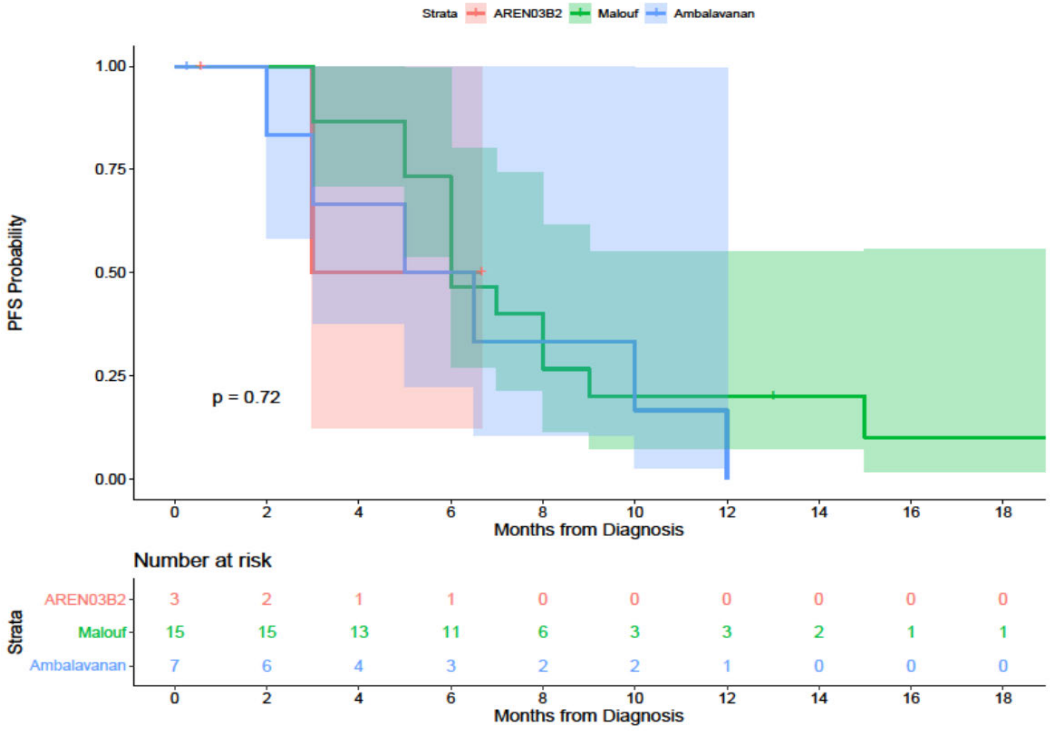
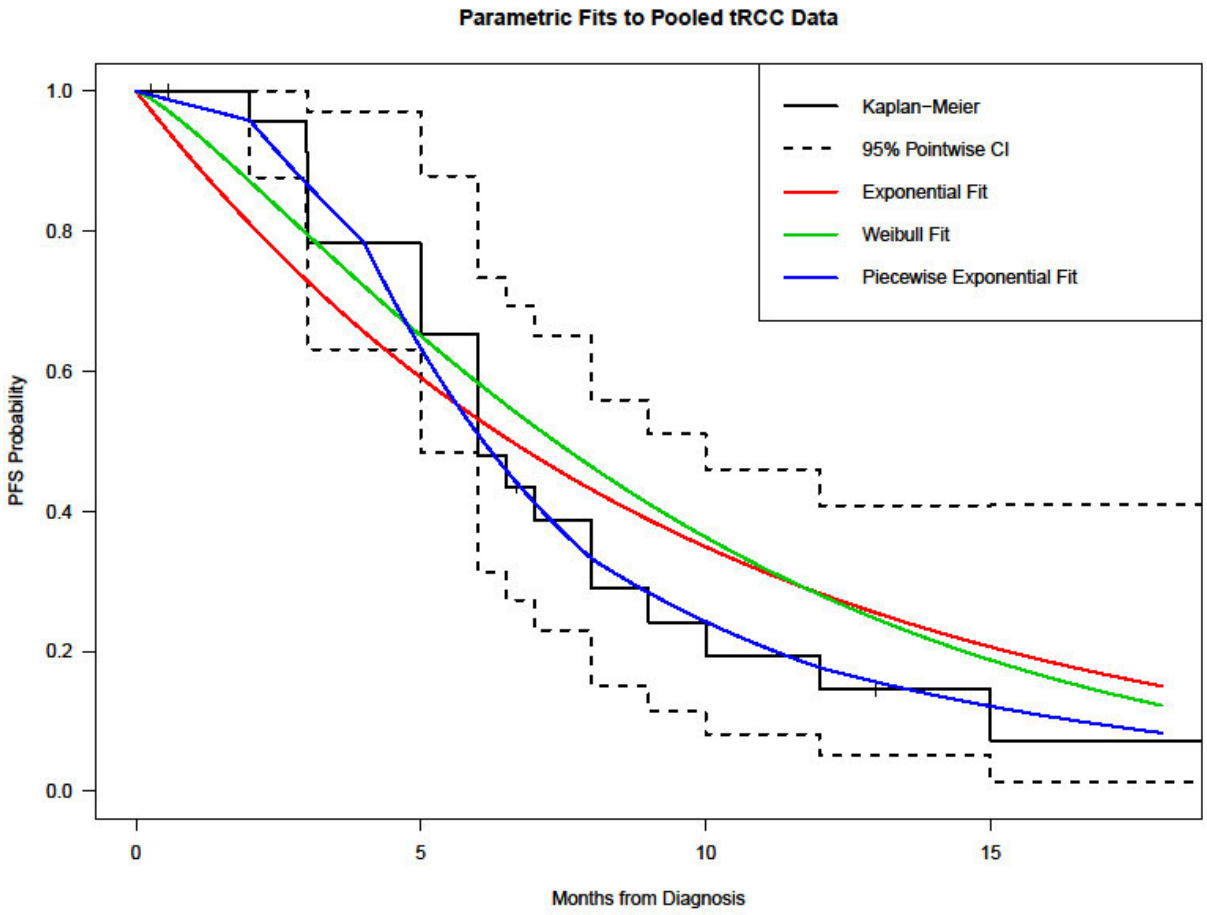


Figure 1B



A comprehensive simulation study was then performed, varying the following: the target sample size and maximum number of events required at the final analysis time point, the number and timing of interim analyses for futility, futility stopping strategies (conditional power under the alternative and current HR), and the true underlying hazard ratio (from HR = 1.0, the null hypothesis type I error scenario, to HR = 0.40, the target alternative hypothesis scenario). For all settings and strategies evaluated in simulations, accrual was assumed to be uniformly distributed as 24 patients per year (as reasoned above, acknowledging that slower than expected accrual will yield greater statistical power than reported here). PFS in the control arm was assumed to follow the piecewise exponential distribution shown in Figure 1B. With 100,000 replicates (simulated trials) used to assess each scenario, we arrived at the following trial design and set of operating characteristics.

The trial will enroll a target of 28 patients to observe 22 PFS events, which are required to achieve at least 80% power to detect a hazard ratio of HR=0.40 using a one-sided stratified log-rank test with alpha = 0.15. If stratum-specific sample sizes allow, stratification of the test will included those factors used for stratification at the time of randomization (age and prior systemic therapy).

The trial will include one formal interim analyses for futility, conducted at 50% (11) of the required 22 PFS events. At this time, an observed hazard ratio greater than 1.00 (i.e., a

trend in the wrong direction) will result in early termination of the trial for futility. The simulated percentage change of early stopping for futility at the planned interim analysis ("early futility), continuing to the final analysis but failing to reach statistical significance ("lack of efficacy"), and continuing to the final analysis and reaching statistical significance ("efficacy") are tabled below for a range of true underlying hazard ratios. Also presented are the average simulated sample size ("Average N") and average simulated time from reopening with Amendment 5A to final trial outcome ("Average Remaining Duration") corresponding to each possible trial outcome. These numbers take into account the patients already enrolled, eligible, and anticipated to be evaluable for the primary endpoint.

True HR	Interim Analysis (50% Events)			Final Analysis (100% Events)			
	Average N	Average Remaining Duration	Early Futility	Lack of Efficacy	Efficacy	Average N	Average Remaining Duration
HR = 1.0	24	9 months	50%	36%	14%	28	17 months
HR = 0.5	25	10 months	15%	19%	66%	28	21 months
HR = 0.4	26	10 months	8%	12%	80%	28	23 months

9.3 Methods of Analysis

Primary Endpoint Analyses

The primary endpoint, progression-free survival, is formally defined in Section 9.4 below. Due to the small size of this trial and the need to preserve alpha-spending for the final analysis, there will be no formal interim analyses of PFS for early efficacy, though this trial will be periodically reviewed by the COG DSMC.

Prospective formal interim analyses for futility will be performed once 50% (11) of the 22 targeted PFS events have been observed. The trial will stop early for futility if, given the data observed to date, the observed hazard ratio for PFS is greater than 1.00, suggesting a trend toward worse outcomes for Arm A (nivolumab + axitinib) compared to Arm C (nivolumab alone).

The final PFS analysis will be performed based on the first quarterly data freeze where at least one of the following criteria are met: (1) a minimum of 2 years of follow-up has been obtained for each patient still "at risk" for a PFS event or (2) when at least 22 PFS events needed for a fully powered final analysis have been confirmed. At this time, a stratified, one-sided log-rank test (using the stratification factors at randomization, age and prior therapy, if stratum-specific sample sizes allow) will be performed to compare treatment arms with alpha = 0.15. A stratified Cox proportional hazards model will also be fit to evaluate the final hazard ratio between the treatment arms (stratification as numbers allow); this will be reported with a 70% confidence interval (to align with the overall alpha level of the primary log-rank test).

While post-progression outcomes on combination therapy among patients who receive crossover upon first progression on the nivolumab-only arm (Arm C) will not be counted toward the primary endpoint analyses, their post-progression experience, including time from first progression to second progression or death (second PFS) will be summarized descriptively.

Secondary Endpoint Analyses

Secondary endpoints OS and ORR (defined in Section 9.4 below) as well as all Grade 3 non-hematologic adverse events and all Grade 4 and higher adverse events will be monitored for data cleanliness and routine reporting as well as formally compared at the time of the final analysis for the primary endpoint, as described below. For ORR and OS below, stratifications factors again may be collapsed and/or omitted depending on the final counts.

ORR: A logistic regression model for overall response, stratified by the stratification factors used at randomization (age and prior therapy) will be fit, including treatment arm as a key covariate. From this model, the odds ratio for treatment arm will be reported with a 70% confidence interval. The ORR observed within each treatment arm will also be reported.

OS: A stratified, one-sided log-rank test (using the stratification factors at randomization, age and prior therapy) will be performed to compare treatment arms with alpha = 0.15. Cox proportional hazards models will also be fit to evaluate the final hazard ratio between the treatment arms, with exploratory modeling taking into account the potential influence of other factors (e.g., baseline disease burden, upfront vs. delayed nephrectomy). From these models, the hazard ratio for treatment assignment will be reported with a 70% confidence interval (to align with the overall alpha level of the primary log-rank test).

AEs: All Grade 3 or higher non-hematologic toxicities and all Grade 4-5 adverse events occurring during protocol therapy or within 100 days of treatment discontinuation, including crossover for patients who receive crossover combination therapy, will be analyzed. The rates of these events will be reported separately by treatment arm (including crossover as a "3rd" arm for this purpose), and both by individual AE and class of AE (e.g., hematologic). Given that some AEs may be rare, Fisher Exact tests will be used to test for statistical significance among any apparent differences by treatment arm.

Exploratory Analyses

Exploratory Aim 1.3.1: To characterize tRCC clinical behavior across all age groups.
We will list and summarize the frequency of site(s) of disease at presentation (including extent of lymph node involvement), site(s) of relapse, surgical practices on protocol therapy, and radiotherapy practices on protocol therapy. We will also summarize the overall response rate (ORR) submitted by the enrolling institution.

Exploratory Aim 1.3.2: To evaluate type of antitumor immune response and stability of T cell activation before and after treatment with immunotherapy or antiangiogenic therapy.
We will summarize the levels of analytes and tumor expression before and after treatment and evaluate the changes due to treatment after logarithmic transformation using the paired t-test. Analytes include myeloid derived stem cells (MDSC): CD45, CD11b, CD33, CD14, CD15, HLA-DR, viability, stain 1; Tregs: viability, CD45, CE4, CD3, CD24, FoxP3; CD8 T cells (CD45, CD8, CD3); CD8 phenotype and activation and exhaustion (CD69, CD38, PD1, CD244, TIM3). Tumor expression of PDL-1, PD1, CD3, CD4 and CD8 will be assessed using TFE RCC samples from the study and scored for intensity (0 – 3).

Exploratory Aim 1.3.4: To characterize the pharmacokinetics of axitinib when given in combination with nivolumab in pediatric patients with tRCC.
The population PK analysis will include all treated patients enrolled beyond Amendment 5A who have at least 1 concentration above the below limit of quantitation (BLQ) in patients treated with axitinib. Pooled PK analysis with another study is to explore the effect of age and body size on axitinib CL/F and Vd/F and make predictions on the dosing of axitinib in pediatric patients in different age groups. Exposure-response relationships will also be explored. The results will be reported separately in a population modeling analysis report. For the purposes of PK analysis, patients who receive crossover therapy will be reported both as a separate cohort and pooled with patients receiving combination therapy up front.

9.4 Endpoints and Evaluability

The primary endpoint is progression-free survival (PFS), which is defined as the time from randomization to the earliest occurrence of disease progression (as defined by modified RECIST criteria for immunotherapy, described in Section 10) or death due to any cause among patients who initiated protocol treatment. Patients not experiencing a PFS event by the time of a prospectively-planned interim or final analysis will be right-censored at the time of their most recent response/progression evaluation. Following the intent-to-treat principle, all patients who are randomized and confirmed to have tRCC by central pathology review will be evaluable for PFS. Patients randomized to Arm B prior to Amendment 2A, and patients who have a central path review confirming a diagnosis other than tRCC, or who never receive central path review per protocol, will be considered inevaluable for the primary endpoint comparison but included in study descriptive statistics.

The overall response rate (ORR) will be defined as the rate of complete or partial responses (assessed by imaging) among patients who initiated protocol therapy and completed at least one subsequent imaging assessment. Patients who are randomized to Arms A or C and are confirmed to have tRCC by central pathology review will be evaluable for ORR.

Overall survival (OS) will be calculated as the time from randomization to death due to any cause, with surviving patients being right-censored at their length of follow-up at the time of analysis. Patients who are randomized to Arms A or C and are confirmed to have tRCC by central pathology review will be evaluable for OS.

Note: For calculations of both PFS and ORR, any lesions resected during protocol therapy for reasons other than progression (as noted by sites or documented upon central surgical review) will not contribute toward response/progression assessments. Response/progression assessments are scheduled to take place after Cycles 2, 4, 6, 9, 12, and then every 4 cycles thereafter, after every cycle following any suspected pseudoprogression until the total tumor burden subsequently diminishes, or at any time clinical progression is suspected. Once in follow-up, patients without a documented PFS event will be evaluated according to the schedule in Section 7.2. ORR and OS will be analyzed as a part of exploratory aim 1.3.1.

9.5 Monitoring Boundary for Dose-Limiting Toxicities

Definitions of DLTs provided in ADVL1315 (for axitinib related DLTs) and ADVL1412 (for PD1-targeting immune checkpoint DLTs) will be used (Section 5.1). DLTs in each arm will be monitored at least weekly to ensure there is no excess toxicity, specifically. No

more than 3 patients (in the first 10 patients treated) experiencing protocol-defined DLTs during the first cycle (4 weeks) of treatment, and no more than 30% of patients experiencing protocol-defined DLTs during the first cycle (4 weeks) of treatment thereafter. Excess toxicities in the combination arm will lead to temporary suspension of accrual so discontinuation or dose reduction may be considered via a formal amendment.

9.6 Gender and Minority Accrual Estimates

The gender and minority distribution of the study population (up to ceiling of 40 patients) is expected to be as follows:

DOMESTIC PLANNED ENROLLMENT REPORT					
Racial Categories	Ethnic Categories				Total
	Not Hispanic or Latino		Hispanic or Latino		
	Female	Male	Female	Male	
American Indian/ Alaska Native	0	0	0	0	**0**
Asian	0	1	0	0	**1**
Native Hawaiian or Other Pacific Islander	0	0	0	0	**0**
Black or African American	6	7	0	0	**13**
White	11	11	2	2	**26**
More Than One Race	0	0	0	0	**0**
Total	**17**	**19**	**2**	**2**	**40**

This distribution was derived from AREN03B2.

10.0 EVALUATION CRITERIA

10.1 Common Terminology Criteria for Adverse Events (CTCAE)

This study will utilize version 5.0 of the CTCAE of the National Cancer Institute (NCI) for toxicity and performance reporting. A copy of the CTCAE version 5.0 can be downloaded from the CTEP website (http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm). Additionally, toxicities are to be reported on the appropriate case report forms.

Please note: 'CTCAE v5.0' is understood to represent the most current version of CTCAE v5.0 as referenced on the CTEP website.

10.2 Response Criteria for Patients with Solid Tumors

Response and progression will be evaluated in this study using the new international criteria proposed by the revised Response Evaluation Criteria in Solid Tumors (RECIST) guideline (version 1.1), with the exceptions described in Section 10.2.1 below to account for possible "pseudoprogression" during treatment with immunotherapy (iRECIST).[62] The major change in iRECIST is the concept of allowing for the possibility of "pseudoprogression", which occurs when standard RECIST v1.1 progression (> 20% increase in tumor burden from baseline) during the first 12 weeks of treatment is followed at the next assessment by tumor shrinkage.[63] Consistent with iRECIST and this definition of pseudoprogression, in the current study, further progression above and beyond the usual 20% threshold will be required to meet the definition of progressive disease for any patient who has not yet completed 12 weeks of protocol therapy.

Following baseline evaluation and treatment initiation, patients should be re-evaluated for lesion response or progression after Cycles 2, 4, 6, 9, 12 and then every 4 cycles thereafter with additional imaging required (1) after every cycle following possible pseudoprogression until subsequent response is documented, and (2) at any time clinical progression is expected. During follow-up, repeat imaging evaluations should occur according to the schedule described in Section 7.2. Confirmatory scans should also be obtained 6-8 weeks (not less than 4 weeks) following initial documentation of objective response.

At each imaging timepoint, the largest diameter (unidimensional measurement) of each target, non-target, or new lesion and the shortest diameter (axis) for each malignant lymph node should be recorded. Any lesions that were surgically resected since the last imaging assessment should be explicitly noted, along with the date and rationale for removal, and an indication of whether the lesion had been increasing in size at the time of surgical removal.

IMPORTANT NOTE: ***All calculations of percentage change in total tumor burden to assess response or progression should fully exclude from consideration any malignant lesions that were surgically resected at any time prior to the most recent response assessment.***

10.2.1 Exceptions for Possible Delayed Response ('Pseudoprogression') – only applicable for patients on Arms A and C

Patients in whom the magnitude of increase in tumor size is ≥ 20% but < 40% from baseline may remain on protocol therapy **for up to 12 weeks after start of protocol therapy** if all of the following criteria are met, to allow for the possibility of pseudoprogression followed by a later tumor response (which may occur during treatment with immunotherapy):

- In the judgment of the treating clinician, the patient does not show evidence for rapid disease progression or the patient has shown evidence for clinical benefit.
- There is no decrease in performance status.
- The patient is tolerating the study drug and there has been no DLT (see Section 5.1).
- Continued treatment with nivolumab alone or in combination with axitinib will not delay an imminent intervention required to prevent a serious complications (e.g. CNS metastases which require radiation therapy or surgery).

For response assessments occurring during the first 12 weeks on protocol therapy, new lesions with a longest diameter of < 10 mm (or newly noted lymph nodes with short axis < 15 mm) should not be counted toward the total tumor burden. Only new lesions with a longest diameter ≥ 10 mm (or lymph nodes with short axis ≥ 15 mm) should be included in the total tumor burden and assessments of percentage change from baseline or nadir.

For patients who remain on protocol therapy despite an increase in tumor burden ≥ 20% (possible pseudoprogression) during the first 12 weeks, imaging to include target lesions must occur every cycle, and the same radiographic and clinical criteria must be met in order to remain on protocol therapy. If tumor burden subsequently diminishes to < 20% increase from baseline or nadir, the patient may

be followed according to the standard protocol guidelines which will involve less frequent imaging. The decision to continue treatment beyond radiographic evidence for disease progression (≥ 20% increase in tumor burden) may be discussed with the study PI and should be documented in the study record.

If at the Week 12 assessment the total tumor burden has not yet diminished to < 20% increase from baseline or nadir, a patient may stay on protocol therapy so long as tumor shrinkage/stabilization continues to occur. If at any point after Week 12 the total tumor burden increases *and* is ≥ 20% from baseline or nadir, this will be defined as progressive disease and the patient must be removed from protocol therapy.

Patients whose best response in the first 12 weeks is pseudoprogression, but who subsequently come off protocol therapy prior to any further assessment, will be considered as having progressive disease. This will include patients who are removed from protocol therapy due to resection of tumor lesions that are increasing in size (see Section 13.1.8.2).

Note: An increase in tumor size of ≥ 40% at any time will be considered true progression and will result in removal from protocol therapy.

10.2.2 Definitions

10.2.2.1 Evaluable for toxicity: All patients will be evaluable for toxicity from the time of their first treatment with axitinib, nivolumab, or the combination of axitinib and nivolumab.

10.2.2.2 Evaluable for objective response: Only those patients who have measurable disease present at baseline, have received at least one cycle of therapy, and have had their disease re-evaluated will be considered evaluable for response. These patients will have their response classified according to the definitions stated below. (**Note:** Patients who exhibit objective disease progression prior to the end of Cycle 1 will also be considered evaluable.)

10.2.2.3 Evaluable non-target disease response: Patients who have lesions present at baseline that are evaluable but do not meet the definitions of measurable disease, have received at least one cycle of therapy, and have had their disease re-evaluated will be considered evaluable for non-target disease. The response assessment is based on the presence, absence, or unequivocal progression of the lesions.

10.2.3 Disease Parameters

10.2.3.1 Measurable disease: Measurable lesions are defined as those that can be accurately measured in at least one dimension (longest diameter to be recorded) as ≥ 20 mm by chest x-ray, as ≥ 10 mm with CT scan, or ≥ 10 mm with calipers by clinical exam. All tumor measurements must be recorded in millimeters (or decimal fractions of centimeters).

Note: Tumor lesions that are situated in a previously irradiated area might or might not be considered measurable in the event that such

lesions have progressed subsequent to such radiation.

10.2.3.2 Malignant lymph nodes: To be considered pathologically enlarged and measurable, a lymph node must be ≥ 15 mm in short axis when assessed by CT scan (CT scan slice thickness recommended to be no greater than 5 mm). At baseline and in follow-up, only the short axis will be measured and followed.

10.2.3.3 Non-measurable disease: All other lesions (or sites of disease), including small lesions (longest diameter < 10 mm or pathological lymph nodes with ≥ 10 to < 15 mm short axis), are considered non-measurable disease. Bone lesions, ascites, pleural/pericardial effusions, lymphangitis cutis/pulmonitis, inflammatory breast disease, and abdominal masses (not followed by CT or MRI), are considered as non-measurable.

Note: Cystic lesions that meet the criteria for radiographically defined simple cysts should not be considered as malignant lesions (neither measurable nor non-measurable) since they are, by definition, simple cysts.

'Cystic lesions' thought to represent cystic metastases can be considered as measurable lesions, if they meet the definition of measurability described above. However, if non-cystic lesions are present in the same patient, these are preferred for selection as target lesions.

10.2.3.4 Target lesions: All measurable lesions up to a maximum of 2 lesions per organ and 5 lesions in total, representative of all involved organs, should be identified as **target lesions** and recorded and measured at baseline. Target lesions should be selected on the basis of their size (lesions with the longest diameter), be representative of all involved organs, but in addition should be those that lend themselves to reproducible repeated measurements. It may be the case that, on occasion, the largest lesion does not lend itself to reproducible measurement in which circumstance the next largest lesion which can be measured reproducibly should be selected. A sum of the diameters (longest for non-nodal lesions, short axis for nodal lesions) for all target lesions will be calculated and reported as the baseline sum diameters. If lymph nodes are to be included in the sum, then only the short axis is added into the sum. The baseline sum diameters will be used as reference to further characterize any objective tumor regression in the measurable dimension of the disease.

10.2.3.5 Non-target lesions: All other lesions (or sites of disease) including any measurable lesions over and above the 5 target lesions should be identified as **non-target lesions** and should also be recorded at baseline. Measurements of these lesions are not required, but the presence, absence, or in rare cases unequivocal progression of each should be noted throughout follow-up.

10.2.4 Methods for Evaluation of Measurable Disease

All measurements should be taken and recorded in metric notation using a ruler or

calipers. All baseline evaluations should be performed as closely as possible to the beginning of treatment and never more than 4 weeks before the beginning of the treatment.

The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during follow-up. Imaging-based evaluation is preferred to evaluation by clinical examination unless the lesion(s) being followed cannot be imaged but are assessable by clinical exam.

10.2.4.1 Clinical lesions: Clinical lesions will only be considered measurable when they are superficial (e.g., skin nodules and palpable lymph nodes) and ≥ 10 mm diameter as assessed using calipers (e.g., skin nodules). In the case of skin lesions, documentation by color photography, including a ruler to estimate the size of the lesion, is recommended.

10.2.4.2 Chest x-ray: Lesions on chest x-ray are acceptable as measurable lesions when they are clearly defined and surrounded by aerated lung. However, CT is preferable.

10.2.4.3 Conventional CT and MRI: This guideline has defined measurability of lesions on CT scan based on the assumption that CT slice thickness is 5 mm or less. If CT scans have slice thickness greater than 5 mm, the minimum size for a measurable lesion should be twice the slice thickness. MRI is also acceptable in certain situations (eg, for body scans).

Use of MRI remains a complex issue. MRI has excellent contrast, spatial, and temporal resolution; however, there are many image acquisition variables involved in MRI, which greatly impact image quality, lesion conspicuity, and measurement. Furthermore, the availability of MRI is variable globally. As with CT, if an MRI is performed, the technical specifications of the scanning sequences used should be optimized for the evaluation of the type and site of disease. Furthermore, as with CT, the modality used at follow-up should be the same as was used at baseline and the lesions should be measured/assessed on the same pulse sequence. It is beyond the scope of the RECIST guidelines to prescribe specific MRI pulse sequence parameters for all scanners, body parts, and diseases. Ideally, the same type of scanner should be used and the image acquisition protocol should be followed as closely as possible to prior scans. Body scans should be performed with breath-hold scanning techniques, if possible.

10.2.4.4 PET-CT: At present, the low dose or attenuation correction CT portion of a combined PET-CT is not always of optimal diagnostic CT quality for use with RECIST measurements. However, if the site can document that the CT performed as part of a PET-CT is of identical diagnostic quality to a diagnostic CT (with IV and oral contrast), then the CT portion of the PET-CT can be used for RECIST measurements and can be used interchangeably with conventional CT in accurately measuring cancer lesions over time. Note, however, that the PET portion of the CT

introduces additional data which may bias an investigator if it is not routinely or serially performed.

10.2.4.5 Ultrasound: Ultrasound is not useful in assessment of lesion size and should not be used as a method of measurement. Ultrasound examinations cannot be reproduced in their entirety for independent review at a later date and, because they are operator dependent, it cannot be guaranteed that the same technique and measurements will be taken from one assessment to the next. If new lesions are identified by ultrasound in the course of the study, confirmation by CT or MRI is advised. If there is concern about radiation exposure at CT, MRI may be used instead of CT in selected instances.

10.2.4.6 Endoscopy, Laparoscopy: The utilization of these techniques for objective tumor evaluation is not advised. However, such techniques may be useful to confirm complete pathological response when biopsies are obtained or to determine relapse in trials where recurrence following complete response (CR) or surgical resection is an endpoint.

10.2.4.7 Cytology, Histology: These techniques can be used to differentiate between partial responses (PR) and complete responses (CR) in rare cases (e.g., residual lesions in tumor types, such as germ cell tumors, where known residual benign tumors can remain).

The cytological confirmation of the neoplastic origin of any effusion that appears or worsens during treatment when the measurable tumor has met criteria for response or stable disease is mandatory to differentiate between response or stable disease (an effusion may be a side effect of the treatment) and progressive disease.

10.2.4.8 FDG-PET: While FDG-PET response assessments need additional study, it is sometimes reasonable to incorporate the use of FDG-PET scanning to complement CT scanning in assessment of progression (particularly possible 'new' disease). New lesions on the basis of FDG-PET imaging can be identified according to the following algorithm:

a. Negative FDG-PET at baseline, with a positive FDG-PET at follow-up is a sign of PD based on a new lesion.
b. No FDG-PET at baseline and a positive FDG-PET at follow-up: If the positive FDG-PET at follow-up corresponds to a new site of disease confirmed by CT, this is PD. If the positive FDG-PET at follow-up is not confirmed as a new site of disease on CT, additional follow-up CT scans are needed to determine if there is truly progression occurring at that site (if so, the date of PD will be the date of the initial abnormal FDG-PET scan). If the positive FDG-PET at follow-up corresponds to a pre-existing site of disease on CT that is not progressing on the basis of the anatomic images, this is not PD.

Note: A 'positive' FDG-PET scan lesion means one which is FDG avid with an uptake greater than twice that of the surrounding tissue on the

attenuation corrected image.

10.2.5 Response Criteria

10.2.5.1 Evaluation of Target Lesions

IMPORTANT: ***All calculations of percentage change in total tumor burden to assess response or progression should fully exclude from consideration any malignant lesions that were surgically resected at any time prior to the latest response assessment.***

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.

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. See Section 10.2.1 for exceptions during the first 12 weeks.

At least a 40% increase in the sum of diameters of target lesions at any time during the study, taking as reference the smallest sum measured on study (this includes the baseline sum if that is the smallest on study).

Appearance of one or more new lesions is also considered progression. See Section 10.2.1 for exceptions during the first 12 weeks.

For patients who achieve a CR, either due to protocol therapy or surgical resection of any remaining malignant lesions, occurrence of a new lesion ≥ 10 mm or the short axis of a lymph node increasing to ≥ 15 mm at any time is considered PD.

An initial response (any decrease in tumor size) followed by growth of at least 20% (relative to the nadir) at any time is considered PD.

Patients who are removed from protocol therapy for resection of lesions that are increasing in size (per Section 13.1.8.2) will be considered to have PD at the time of tumor resection.

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.

10.2.5.2 Evaluation of Non-Target Lesions

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

Note: If tumor markers are initially above the upper normal limit, they must normalize for a patient to be considered in complete clinical response.

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 (see Section 10.2.1 for exceptions) 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 only "non-target" lesions is exceptional, the opinion of the treating physician should prevail in such circumstances.

10.2.5.3 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-	No	SD	documented at least

	PD/not evaluated			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 for further details on what is evidence of a new lesion.
** Only for non-randomized trials with response as primary endpoint.
*** In exceptional circumstances, unequivocal progression in non-target lesions may be accepted as disease progression.
[#] See Section 10.2.1 for exceptions for pseudoprogression during the first 12 weeks of protocol therapy.

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.

10.2.6 Duration of Response

10.2.6.1 Duration of overall response: The duration of overall response is measured from the time measurement criteria are met for CR or PR (whichever is first recorded) until the first date that recurrent or progressive disease is objectively documented (taking as reference for progressive disease the smallest measurements recorded since the treatment started).

The duration of overall CR is measured from the time measurement criteria are first met for CR until the first date that progressive disease is objectively documented.

10.2.6.2 Duration of stable disease: Stable disease is measured from the start of the treatment until the criteria for progression are met, taking as reference the smallest measurements recorded since the treatment started, including the baseline measurements.

10.2.7 Progression-Free Survival

PFS is defined as the duration of time from randomization to the earlier of progression (as defined in this section) or death due to any cause.

11.0 ADVERSE EVENT REPORTING REQUIREMENTS

11.1 Purpose

Adverse event (AE) 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. Certain adverse events must be reported in an expedited manner to allow for timelier monitoring of patient safety and care. The following sections provide information about expedited reporting.

11.2 Expedited Reporting Requirements – Serious Adverse Events (SAEs)

To ensure compliance with these regulations/this guidance, as IND/IDE sponsor, NCI requires that AEs be submitted according to the timeframes in the AE reporting table

assigned to the protocol (Section 11.8), using the CTEP Adverse Event Reporting System (CTEP-AERS).

Any AE that is serious qualifies for expedited reporting. An AE is defined as any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related. A Serious Adverse Event (SAE) is any adverse drug event (experience) occurring at any dose that results in ANY of the following outcomes:

1) Death.
2) A life-threatening adverse drug experience.
3) An adverse event resulting in inpatient hospitalization or prolongation of existing hospitalization (for ≥ 24 hours). This does not include hospitalizations that are part of routine medical practice.
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 a serious adverse drug experience 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.

11.3 Specific Examples for Expedited Reporting

11.3.1 SAEs Occurring More than 30 Days After Last Dose of Study Drug

Any Serious Adverse Event that occurs more than 30 days after the last administration of the investigational agent/intervention **and** has an attribution of a possible, probable, or definite relationship to the study therapy must be reported according to the CTEP-AERS reporting table in this protocol (Section 11.8).

11.3.2 Persistent or Significant Disabilities/Incapacities

Any AE that results in persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions (formerly referred to as disabilities), congenital anomalies or birth defects, must be reported via CTEP-AERS if it occurs at any time following treatment with an agent under a NCI IND/IDE since these are considered serious AEs.

11.3.3 Death

Reportable Categories of Death

- Death attributable to a CTCAE term.
- Death Neonatal: Newborn death occurring during the first 28 days after birth.
- Sudden Death NOS: A sudden (defined as instant or within one hour of the onset of symptoms) or an unobserved cessation of life that cannot be attributed to a CTCAE term associated with Grade 5.
- Death NOS: A cessation of life that cannot be attributed to a CTCAE term associated with Grade 5.
- 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.

11.3.4 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 metastasis of the initial neoplasm is not considered a secondary malignancy.

The NCI 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
- Myelodysplastic syndrome
- Treatment related secondary malignancy

Any malignancy possibly related to cancer treatment (including AML/MDS) must also be reported via the routine reporting mechanisms outlined in this protocol.

11.3.5 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.

11.3.6 Pregnancy, Pregnancy Loss, and Death Neonatal

NOTE: When submitting CTEP-AERS reports for "Pregnancy", "Pregnancy loss", or "Death Neonatal", the Pregnancy Information Form, available at: http://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/PregnancyReportForm.pdf, needs to be completed and faxed along with any additional medical information to (301) 897-7404. The potential risk of exposure of the fetus to the investigational agent(s) or chemotherapy agent(s) should be documented in the "Description of Event" section of the CTEP-AERS report.

11.3.6.1 **Pregnancy**

Patients who become pregnant on study risk intrauterine exposure of the fetus to agents that may be teratogenic. For this reason, pregnancy needs to be reported in an expedited manner via CTEP-AERS as **Grade 3 "*Pregnancy, puerperium and perinatal conditions - Other (pregnancy)*"** under the "***Pregnancy, puerperium and perinatal conditions"*** SOC.

Pregnancy needs to be followed **until the outcome is known**. If the baby is born with a birth defect or anomaly, then a second CTEP-AERS report is required.

11.3.6.2 **Pregnancy Loss (Fetal 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**. Do NOT report a pregnancy loss as a Grade 5 event since CTEP-AERS recognizes any Grade 5 event as a patient death.

11.3.6.3 **Death Neonatal**

Neonatal death, defined in CTCAE as *"Newborn death occurring during the first 28 days after birth*" should be reported expeditiously, as **Grade 4 *"Death neonatal" under the* "*General disorders and administration*" SOC when the death is the result of a patient pregnancy or pregnancy in partners of men on study**. Do NOT report a neonatal death resulting from a patient pregnancy or pregnancy in partners of men on study as a Grade 5 event since CTEP-AERS recognizes any Grade 5 event as a patient death.

11.4 Reporting Requirements for Specialized AEs

11.4.1 Baseline AEs

Although a pertinent positive finding identified on baseline assessment is not an AE, when possible it is to be documented as "Course Zero" using CTCAE terminology and grade. An expedited AE report is not required if a patient is entered on a protocol with a pre-existing condition (e.g., elevated laboratory value, diarrhea). The baseline AE must be re-assessed throughout the study and reported if it fulfills expedited AE reporting guidelines.

a. If the pre-existing condition worsens in severity, the investigator must reassess the event to determine if an expedited report is required.
b. If the AE resolves and then recurs, the investigator must re-assess the event to determine if an expedited report is required.
c. No modification in grading is to be made to account for abnormalities existing at baseline.

11.4.2 Persistent AEs

A persistent AE is one that extends continuously, without resolution between treatment cycles/courses.

ROUTINE reporting: The AE must be reported only once unless the grade becomes more severe in a subsequent course. If the grade becomes more severe the AE must be reported again with the new grade.

EXPEDITED reporting: The AE must be reported only once unless the grade becomes more severe in the same or a subsequent course.

11.4.3 Recurrent AEs

A recurrent AE is one that occurs and resolves during a cycle/course of therapy and then reoccurs in a later cycle/course.

ROUTINE reporting: An AE that resolves and then recurs during a subsequent cycle/course must be reported by the routine procedures.

EXPEDITED reporting: An AE that resolves and then recurs during a subsequent cycle/course does not require CTEP-AERS reporting unless:

1) The grade increases OR
2) Hospitalization is associated with the recurring AE.

11.5 Exceptions to Expedited Reporting

11.5.1 Specific Protocol Exceptions to Expedited Reporting (SPEER)

SPEER: Is a subset of AEs within the Comprehensive Adverse Events and Potential Risks (CAEPR) that contains a list of events that are considered expected for CTEP-AERS reporting purposes. (Formerly referred to as the Agent Specific Adverse Event List (ASAEL).)

AEs listed on the SPEER should be reported expeditiously by investigators to the NCI via CTEP-AERS ONLY if they exceed the grade of the event listed in parentheses after the event. If the CAEPR is part of a combination IND using multiple investigational agents and has an SAE listed on different SPEERs, use the lower of the grades to determine if expedited reporting is required.

11.5.2 Special Situations as Exceptions to Expedited Reporting

An expedited report may not be required for a specific protocol where an AE is listed as expected. The exception or acceptable reporting procedures will be specified in the protocol. The protocol specific guidelines supersede the NCI Adverse Event Reporting Guidelines. These special situations are listed in Section 11.9 of this protocol.

11.6 Reporting Requirements - Investigator Responsibility

Clinical investigators in the treating institutions and ultimately the Study Chair have the primary responsibility for AE identification, documentation, grading, and assignment of attribution to the investigational agent/intervention. It is the responsibility of the treating physician to supply the medical documentation needed to support the expedited AE reports in a timely manner.

Note: All expedited AEs (reported via CTEP-AERS) must also be reported via routine reporting. Routine reporting is accomplished via the Adverse Event (AE) Case Report Form (CRF) within the study database.

11.7 General Instructions for Expedited Reporting via CTEP-AERS

The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 will be utilized for AE reporting. All appropriate treatment areas should have access to a copy of the CTCAE version 5.0. A copy of the CTCAE version 5.0 can be downloaded from the CTEP website at: http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm.

An expedited AE report for all studies utilizing agents under an NCI IND/IDE must be submitted electronically to NCI via CTEP-AERS at: https://eapps-ctep.nci.nih.gov/ctepaers

In the rare situation where Internet connectivity is disrupted, the 24-hour notification is to be made to the NCI for agents supplied under a CTEP IND by telephone call to (301) 897-7497.

In addition, once Internet connectivity is restored, a 24-hour notification that was phoned in must be entered into the electronic CTEP-AERS system by the original submitter of the report at the site.

- Expedited AE reporting timelines are defined as:
  - **24-Hour; 5 Calendar Days -** The AE must initially be reported via CTEP-AERS within 24 hours of learning of the event, followed by a complete expedited report within 5 calendar days of the initial 24-hour report.
  - **7 Calendar Days -** A complete expedited report on the AE must be submitted within 7 calendar days of the investigator learning of the event.

- Any event that results in a persistent or significant incapacity/substantial disruption of the ability to conduct normal life functions, or a congenital anomaly/birth defect, or is an IME, which based upon the medical judgment of the investigator may jeopardize the patient and require intervention to prevent a serious AE, must be reported via CTEP-AERS **if the event occurs following investigational agent administration.**
- Any death occurring within 30 days of the last dose, regardless of attribution to an agent/intervention under an NCI IND/IDE requires expedited reporting **within 24 hours**.
- Any death occurring greater than 30 days of the last dose with an attribution of possible, probable, or definite to an agent/intervention under an NCI IND/IDE requires expedited reporting **within 24 hours**.

CTEP-AERS Medical Reporting includes the following requirements as part of the report: 1) whether the patient has received at least one dose of an investigational agent on this study; 2) the characteristics of the adverse event including the *grade* (severity), the *relationship to the study therapy* (attribution), and the *prior experience* (expectedness) of the adverse event; 3) the Phase (1, 2, or 3) of the trial; and 4) whether or not hospitalization or prolongation of hospitalization was associated with the event.

Any medical documentation supporting an expedited report (eg, H & P, admission and/or notes, consultations, ECG results, etc.) MUST be faxed within 48-72 hours to the NCI. NOTE: English is required for supporting documentation submitted to the numbers listed below in order for the NCI to meet the regulatory reporting timelines.

Fax supporting documentation **for AEs related to investigational agents supplied under a CTEP IND** to: (301) 897-7404.

Also: Fax or email supporting documentation to COG for **all** IND studies (Fax# (310) 640-9193; email: COGAERS@childrensoncologygroup.org; Attention: COG AERS Coordinator).

- **ALWAYS include the ticket number on all faxed documents.**
- **Use the NCI protocol number and the protocol-specific patient ID provided during trial registration on all reports.**

11.8 Reporting Table for 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]

**** Note expanded reporting timeframe of 100 days for AEs related to nivolumab (see Section 11.9.3)**

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) Any AE that results in inpatient hospitalization or prolongation of existing hospitalization for ≥ 24 hours. This does not include hospitalizations that are part of routine medical practice.
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 CTEP-AERS 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="3">7 Calendar Days</td><td rowspan="2">24-Hour Notification 5 Calendar Days</td></tr>
<tr><td>Not resulting in Hospitalization ≥ 24 hrs</td><td colspan="2">Not Required</td><td>7 Calendar Days</td></tr>
</table>

NOTE: Protocol specific exceptions to expedited reporting of serious adverse events are found in the Specific Protocol Exceptions to Expedited Reporting (SPEER) portion of the CAEPR. Additional Special Situations as Exceptions to Expedited Reporting are listed below.

Expedited AE reporting timelines are defined as:

"24-Hour; 5 Calendar Days" - The AE must initially be reported via CTEP-AERS within 24 hours of learning of the AE, followed by a complete expedited report within 5 calendar days of the initial 24-hour notification.

"7 Calendar Days" - A complete expedited report on the AE must be submitted within 7 calendar days of learning of the AE.

[1]SAEs that occur more than 30 days after the last administration of investigational agent/intervention axitinib or more than 100 days after the last administration of investigational agent/intervention nivolumab, 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 7 calendar day reports for:

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

11.9 Protocol Specific Additional Instructions and Reporting Exceptions

11.9.1 Grades 1-2 myelosuppression (anemia, neutropenia, and thrombocytopenia) do not require expedited reporting.

11.9.2 Hospitalization for surgery to resect tumor, primary or metastatic, will not be considered an SAE.

11.9.3 For patients who receive nivolumab as part of this study, reporting of immune related AEs (IMAEs) via CTEP-AERS must continue up to 100 days post last dose of nivolumab.

11.10 Routine Reporting of Adverse Events

NOTE: The guidelines below are for routine reporting of study specific adverse events on the COG case report forms and do not affect the requirements for CTEP-AERS reporting.

Routine reporting is accomplished via the Adverse Event (AE) Case Report Form (CRF) within the study database. For this study, routine reporting will include all CTEP-AERS reportable events, all DLTs (see Section 5.1), and all Grade 3 and higher Adverse Events.

NOTE: For patients who receive nivolumab as part of this study, routine reporting of immune related AEs (IMAEs) must continue up to 100 days post last dose of nivolumab.

12.0 STUDY REPORTING AND MONITORING

The Case Report Forms and the submission schedule are posted on the COG web site with each protocol under "*Data Collection/Specimens*". A submission schedule is included.

12.1 CDUS

This study will be monitored by the Clinical Data Update System (CDUS) Version 3.0. Cumulative protocol- and patient-specific CDUS data will be submitted quarterly to CTEP by electronic means. Reports are due January 31, April 30, July 31 and October 31. CDUS reporting is not a responsibility of institutions participating in this trial.

12.2 Data and Safety Monitoring Committee

To protect the interests of patients and the scientific integrity for all clinical trial research by the Children's Oncology Group, the COG Data and Safety Monitoring Committee (DSMC) reviews reports of interim analyses of study toxicity and outcomes prepared by the study statistician, in conjunction with the study chair's report. The DSMC may recommend the study be modified or terminated based on these analyses.

Toxicity monitoring is also the responsibility of the study committee and any unexpected frequency of serious events on the trial are to be brought to the attention of the DSMC. The study statistician is responsible for the monitoring of the interim results and is expected to request DSMC review of any protocol issues s/he feels require special review. Any COG member may bring specific study concerns to the attention of the DSMC.

The DSMC approves major study modifications proposed by the study committee prior to implementation (e.g., termination, dropping an arm based on toxicity results or other trials reported, increasing target sample size, etc.). The DSMC determines whether and to whom outcome results may be released prior to the release of study results at the time specified in the protocol document.

12.3 CRADA/CTA

The agent(s) supplied by CTEP, DCTD, NCI used in this protocol is/are provided to the NCI under a Collaborative Agreement (CRADA, CTA, CSA) between the Pharmaceutical Company(ies) (hereinafter referred to as "Collaborator(s)") and the NCI Division of Cancer Treatment and Diagnosis. Therefore, the following obligations/guidelines, in addition to the provisions in the "Intellectual Property Option to Collaborator" (http://ctep.cancer.gov/industryCollaborations2/intellectual_property.htm) contained within the terms of award, apply to the use of the Agent(s) in this study:

1. Agent(s) may not be used for any purpose outside the scope of this protocol, nor can Agent(s) be transferred or licensed to any party not participating in the clinical study. Collaborator(s) data for Agent(s) are confidential and proprietary to Collaborator(s) and shall be maintained as such by the investigators. The protocol documents for studies utilizing Agents contain confidential information and should not be shared or distributed without the permission of the NCI. If a copy of this protocol is requested by a patient or patient's family member participating on the study, the individual should sign a confidentiality agreement. A suitable model agreement can be downloaded from: http://ctep.cancer.gov.

2. For a clinical protocol where there is an investigational Agent used in combination with (an)other Agent(s), each the subject of different Collaborative Agreements, the access to and use of data by each Collaborator shall be as follows (data pertaining to such combination use shall hereinafter be referred to as "Multi-Party Data"):

    a. NCI will provide all Collaborators with prior written notice regarding the existence and nature of any agreements governing their collaboration with NCI, the design of the proposed combination protocol, and the existence of any obligations that would tend to restrict NCI's participation in the proposed combination protocol.

    b. Each Collaborator shall agree to permit use of the Multi-Party Data from the clinical trial by any other Collaborator solely to the extent necessary to allow said other Collaborator to develop, obtain regulatory approval or commercialize its own Agent.

    c. Any Collaborator having the right to use the Multi-Party Data from these trials must agree in writing prior to the commencement of the trials that it will use the Multi-Party Data solely for development, regulatory approval, and commercialization of its own Agent.

3. Clinical Trial Data and Results and Raw Data developed under a Collaborative Agreement will be made available to Collaborator(s), the NCI, and the FDA, as appropriate and unless additional disclosure is required by law or court order as described in the IP Option to Collaborator (http://ctep.cancer.gov/industryCollaborations2/intellectual_property.htm).

Additionally, all Clinical Data and Results and Raw Data will be collected, used and disclosed consistent with all applicable federal statutes and regulations for the protection of human subjects, including, if applicable, the *Standards for Privacy of Individually Identifiable Health Information* set forth in 45 C.F.R. Part 164.

4. When a Collaborator wishes to initiate a data request, the request should first be sent to the NCI, who will then notify the appropriate investigators (Group Chair for Cooperative Group studies, or PI for other studies) of Collaborator's wish to contact them.

5. Any data provided to Collaborator(s) for Phase 3 studies must be in accordance with the guidelines and policies of the responsible Data Monitoring Committee (DMC), if there is a DMC for this clinical trial.

6. Any manuscripts reporting the results of this clinical trial must be provided to CTEP by the Group office for Cooperative Group studies or by the principal investigator for non-Cooperative Group studies for immediate delivery to Collaborator(s) for advisory review and comment prior to submission for publication. Collaborator(s) will have 30 days from the date of receipt for review. Collaborator shall have the right to request that publication be delayed for up to an additional 30 days in order to ensure that Collaborator's confidential and proprietary data, in addition to Collaborator(s)'s intellectual property rights, are protected. Copies of abstracts must be provided to CTEP for forwarding to Collaborator(s) for courtesy review as soon as possible and preferably at least three (3) days prior to submission, but in any case, prior to presentation at the meeting or publication in the proceedings. Press releases and other media presentations must also be forwarded to CTEP prior to release. Copies of any manuscript, abstract and/or press release/media presentation should be sent to:

   Email: ncicteppubs@mail.nih.gov

   The Regulatory Affairs Branch will then distribute them to Collaborator(s). No publication, manuscript or other form of public disclosure shall contain any of Collaborator's confidential/ proprietary information.

13.0 SURGICAL GUIDELINES

Timing of protocol therapy administration, response assessment studies, and surgical interventions are based on schedules derived from the experimental design or on established standards of care. Minor unavoidable departures (up to 72 hours) from protocol directed therapy and/or disease evaluations (and up to 1 week for surgery) for valid clinical, patient and family logistical, or facility, procedure and/or anesthesia scheduling issues are acceptable (except where explicitly prohibited within the protocol).

13.1 Surgical Principles

13.1.1 Study Inclusion Criteria

This study is designed to study patients with histologically confirmed, unresectable or metastatic translocation morphology renal cell carcinoma diagnosed using WHO-defined criteria who also have measurable disease as defined by RECIST

v1.1 and an inability to undergo complete resection of the disease by surgery. Therefore, patients eligible for this study must have histological confirmation of disease either by biopsy, nephrectomy or metastectomy and after this diagnostic surgery still have remaining, measurable disease. The decision about the resectability of remaining disease is left to the treating institution.

13.1.2 Cytoreductive Nephrectomy

Cytoreductive nephrectomy is not required for patient enrollment; however, we encourage cytoreductive nephrectomy when feasible. Level I evidence from the prior immune-modulatory era (cytokine era) for treating metastatic renal cell carcinoma demonstrated the survival benefit of cytoreductive nephrectomy.[64, 65] While we await randomized-trial data about the impact of cytoreductive nephrectomy in the current era of targeted therapy for metastatic renal cell carcinoma, analyses of retrospective and administrative data suggest that it may be beneficial in select patients.[66, 67] Therefore, when possible we would encourage cytoreductive nephrectomy prior to beginning protocol therapy. Per Section 3.2.8.3, patients must be more than 7 days out from major surgery (which includes open or laparoscopic nephrectomy) for eligibility. For the purposes of this study cytoreductive nephrectomy may include radical or partial nephrectomy and may be achieved by either an open or laparoscopic approach. Additionally, delayed cytoreductive nephrectomy is permitted 12 weeks after starting protocol therapy, taking into account the need for holding axitinib before and after nephrectomy per Section 13.1.8.3.

13.1.3 Primary Nephrectomy

In many children and adolescents with translocation morphology renal cell carcinoma, their histologic diagnosis will be unknown at the time of primary nephrectomy since the vast majority of patients in this age group have a non-renal cell carcinoma histology such as Wilms tumor. The impact of this is that the surgical approach to these patients varies since in many cases the pre-operative assumption is that the tumor in question represents Wilms tumor compared to adults with renal tumors where the vast majority have renal cell carcinoma. Therefore, the surgical guidelines to renal tumors in children and adolescents are directed towards managing Wilms tumor and below we will outline these general guidelines which will also be sufficient for the surgical approach to managing those with renal cell carcinoma.

A generous transabdominal, transperitoneal or thoracoabdominal incision is recommended for adequate exposure. Complete exploration of the abdomen should be performed. A radical nephrectomy is performed with the ureter divided as distally as possible**.** Routine exploration of the contralateral kidney is not necessary if imaging is satisfactory and does not suggest a bilateral process.

The lateral peritoneal reflection is opened, and the colon is reflected medially. A plane is established outside of Gerota's fascia by sharp and blunt dissection. Before mobilizing the primary tumor, an attempt should be made to dissect, expose and ligate the renal vessels in order to lessen the chance of hematogenous spread of tumor cells while removing the tumor**. Preliminary ligation should not be pursued if technically difficult or dangerous.** The **adrenal gland** may be left in place if it is not abutting the tumor; but, if the mass arises in the upper pole of the

kidney, the adrenal gland should be removed with the neoplasm. The **ureter** is ligated and divided as low as conveniently possible, but it is not necessary to remove the ureter completely. The tumor and the uninvolved portion of the kidney are mobilized and removed intact.

The use of titanium clips is strongly recommended to identify gross residual tumor. Clips should not be used for hemostasis and those placed for roentgenographic identification or radiation therapy portals should be limited to the minimum number necessary. Metallic clips can interfere with the CT scan. Clips are best applied by placing a non-absorbable suture in the structure to be marked, and attaching the clip to the suture. In general four small clips should be sufficient to delineate the margins of the tumor.

Any suspicious areas that represent metastases should be biopsied, the site(s) identified with small titanium clips so that the locations can be determined later by roentgenograms. The specimen should be specifically identified as to the site from which it was removed.

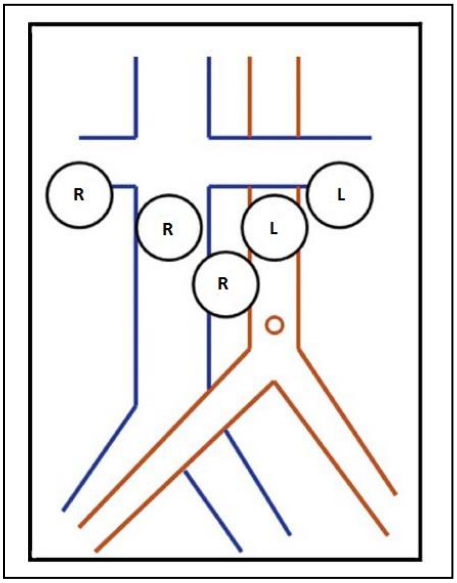
13.1.4 Partial Nephrectomy

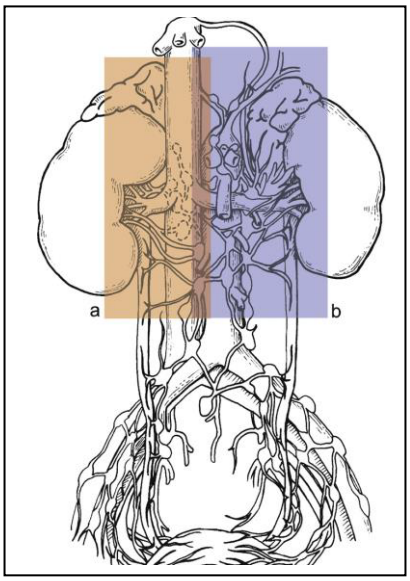
While partial nephrectomy in adult patients is commonly approached through a variety of incisions including open flank, open transperitoneal and minimally invasively, in children undergoing partial nephrectomy, we recommend a transperitoneal incision. Additionally, even though not planned as a radical nephrectomy, the surgeon should inspect the renal hilar and periaortic area and sample lymph nodes as recommended per radical nephrectomy to rule out lymphatic spread. Palpate the renal vein and IVC for evidence of tumor extension. Do not biopsy the tumor if a partial nephrectomy with margins can be performed since this is a criterion for local Stage III designation if the ultimate pathology is determined to be Wilms tumor. Avoid rupture or spillage by use of an adequate incision. Control of the renal vessels is recommended, but the surgery can generally be performed without hypothermia or vascular ischemia. In most children, manual compression of the kidney can be used to control bleeding during the dissection. Gerota's fascia is opened and the perirenal fat is dissected off the renal surface excluding the fat attached to the mass. A circumferential incision of the renal capsule around the surface of the tumor should be performed and the capsule peeled back to expose the adjacent renal parenchyma. A wedge or guillotine resection of the tumor is performed. The tumor should be excised with a 0.5 to 1 cm rim of normal parenchyma. After removal of the tumor any bleeding vessels can be suture ligated with absorbable suture. If there is transection of the collecting system, a watertight closure with fine absorbable suture is recommended. If renorraphy is required this can be done by bringing the parenchyma back over the defect anchoring the sutures in the renal capsule.

During the mobilization of the kidney and during dissection of the tumor, care must be taken not to place traction on the renal vessels. The small vessels in these young patients are prone to intimal injury which can lead to spasm and subsequent thrombosis.

13.1.5 Surgical Management of Lymph Nodes at the Time of Nephrectomy

While there are no randomized clinical trial data to demonstrate that an extended lymph node dissection is mandated in patients with Wilms tumor or pediatric Renal Cell Carcinoma, there are data that insufficient surgical nodal staging may negatively impact outcomes in both diseases.[68-71] Therefore, we encourage removal of nodal tissue in the anatomic drainage areas for the respective kidneys (see anatomic map below adapted from Crispen et al.[72] and Capitano et al.[73]). The superior, inferior and lateral edges of these nodal templates should be controlled with suture ties and if needed, very selective use of titanium clips. The nodes should be carefully labeled by anatomic region for separate microscopic examination. The anatomic boundaries of these nodal drainage basins are as per Capitano et al.[73]: "Lymph node drainage for the ***right*** kidney includes the paracaval, retrocaval, precaval, and interaortocaval nodes from the adrenal vein to the level of the inferior mesenteric artery, and for the ***left*** kidney includes the para-aortic and preaortic nodes from the crus of the diaphragm to the inferior mesenteric artery."





13.1.6 Surgical Management of Venous Tumor Thrombus

Renal tumors extend as venous tumor thrombi into the renal vein and potentially the inferior vena cava and even atrium in 5-10% of cases. If preoperative imaging suggests a venous tumor thrombus but cannot adequately detail its extent for preoperative planning, preoperative sonography or magnetic resonance imaging may be helpful. Intraoperatively, the renal vein and inferior vena cava should be palpated carefully before ligation to rule out extension of the tumor into the wall or the lumen of the vein. If tumor extension is present, this should be removed *en bloc* with the kidney, if possible. Note should be made of whether tumor penetrates the vessel wall or is attached to the intima.

The tumor that extends into the renal vein and cava may simply extend as a floating attachment and can then be ―fished out. Control of the renal vein and cava above and below the tumor with vessel loops or umbilical tape is necessary. The tumor and kidney should be completely mobilized prior to removing vascular thrombus.

A venotomy is then done and the tumor pulled out of the vein. A Foley balloon technique can also be used to pull out the tumor. The tumor should not be transected. In other instances the tumor may be fixed to the vascular lumen. Extraction is more difficult and a larger venotomy may be required. A similar technique used for removing plaque for a carotid endarterectomy is helpful to lift the tumor off the vein wall. If the tumor extends above the hepatic veins, cardiopulmonary bypass may be needed to remove the vascular extent of the tumor. The abdominal tumor is mobilized and removed first prior to administration of heparin. After placing the child on bypass the right atrium is opened and the tricuspid value inspected. The tumor is removed from the heart above and below at the same time to prevent tumor emboli.

13.1.7 Biopsy

For trial eligibility, biopsy of the primary tumor or sites of metastasis are acceptable for histologic confirmation of translocation morphology renal cell carcinoma. Biopsy may be done either via open or percutaneous needle approaches. Biopsy (whether needle biopsy or open biopsy) mandates waiting 7 days prior to study enrollment.

A word of caution for children undergoing biopsy of the primary mass, if this reveals a diagnosis of Wilms tumor then they will be mandatorily staged as a local Stage III which includes treatment intensification with doxorubicin and radiation therapy. Thus, biopsy in these cases should be undertaken only after considering such therapeutic implications.

13.1.8 On Protocol Surgery

13.1.8.1 Restrictions During the First 12 Weeks of Therapy

Due to the need to assess tumor response to therapy, no surgical tumor resection is permitted during the first 12 weeks of protocol therapy. Patients who undergo surgery for tumor resection during this period must be removed from protocol therapy.

13.1.8.2 Restrictions for Patients with Tumor Growth

Any surgical tumor resection performed for lesions that are increasing in size (any increase in size based on radiology) will result in removal from protocol therapy.

13.1.8.3 Cytoreductive Nephrectomy During Therapy

Patients who have not had cytoreductive nephrectomy prior to trial enrollment but who elect to have cytoreductive nephrectomy during therapy must hold axitinib for 7 days before surgery and wait 7 days after surgery to restart axitinib.

13.1.8.4 Elective Surgery

Patients undergoing a major, elective surgical procedure must hold axitinib for 7 days before surgery and wait 7 days after surgery to restart axitinib.

13.1.8.5 Emergency Surgery

For an emergency, axitinib must be held for 7 days after surgery.

13.2 Staging of Renal Cell Carcinoma

American Joint Committee on Cancer (AJCC) – TNM Staging System for Kidney Cancer (7th Ed., 2010)[74]

13.2.1 Primary Tumor (T)

- Tx – Primary tumor cannot be assessed
- T0 – No evidence of primary tumor
- T1 – Tumor 7 cm or less in greatest dimension, limited to the kidney
  - T1a – Tumor 4 cm or less in greatest dimension, limited to the kidney
  - T1b – Tumor more than 4 cm but not more than 7 cm in greatest dimension, limited to the kidney
- T2 – Tumor more than 7cm in greatest dimension, limited to the kidney
  - T2a – Tumor more than 7cm but less than or equal to 10cm in greatest dimension, limited to the kidney
  - T2b – Tumor more than 10cm in greatest dimension, limited to the kidney
- T3 – Tumor extends into major veins or perinephric tissues but not into the ipsilateral adrenal gland and not beyond Gerota's fascia
  - T3a – Tumor grossly extends into the renal vein or its segmental (muscle containing) branches, or tumor invades perirenal and/or renal sinus fat but not beyond Gerota's fascia
  - T3b – Tumor grossly extends into the vena cava below the diaphragm
  - T3c – Tumor grossly extends into the vena cava above the diaphragm or invades the wall of the vena cava
- T4 – Tumor invades beyond Gerota's fascia (including contiguous extension into the ipsilateral adrenal gland)

13.2.2 Regional Lymph Nodes (N)

- Nx – Regional lymph nodes cannot be assessed
- N0 – No regional lymph node metastasis
- N1 – Metastasis in regional lymph node(s)

13.2.3 Distant Metastasis (M)

- M0 – No distant metastasis
- M1 – Distant metastasis

Table 4. Anatomic Stage Group

	T	N	M
Stage I	T1	N0/Nx	M0
Stage II	T2	N0/Nx	M0
Stage III	Tx, T0, T1, T2 T3	N1 Any N	M0 M0
Stage IV	T4 Any T	Any N Any N	M0 M1

13.3 Surgical Specimens

Institutions are required to submit samples of diagnostic tumor tissue for retrospective central pathology review on this study (see Section 14.1.1). In addition, submission of tumor tissue from diagnosis and from subsequent surgical procedures for banking is strongly encouraged (see Section 15.2.3). All tumor specimens removed should be presented to the pathologist fresh or in saline, rather than fixed in formalin. Specimens should be transported to pathology immediately after removal to allow sampling of fresh tissue for molecular biology studies. Notification of the pathology laboratory in advance will facilitate proper specimen collections.

14.0 PATHOLOGY GUIDELINES AND SPECIMEN REQUIREMENTS

14.1 Institutional Pathology Requirements

14.1.1 Retrospective Central Review of Diagnostic Samples:

All patients enrolling on this protocol will undergo a retrospective central pathology review to confirm histologic classification. The results of this review will not be returned to the referring institution.

14.1.2 Required Special Studies:

In order to be eligible for this study, the institution must confirm either TFE3 nuclear protein expression by immunohistochemistry or evidence of TFE3 or TFEb translocation by either FISH or RT-PCR in a CLIA-certified laboratory. Institutions may choose to submit unstained slides directly to Dr. Elizabeth Perlman, who will perform TFE3 analysis at no charge. See Section 14.5 for Dr. Perlman's contact information. The slide will be returned to the referring institution for local evaluation, to be included in their institutional report. Please note that this is separate from a consultation for a difficult case, for which a fee may be charged. The slide(s) for consultation should be sent directly to Dr. Perlman and not to the Biopathology Center.

14.2 Tissue Specimens/Pathology Review at Time of Diagnosis

All patients enrolling on this protocol require institutional histological confirmation of translocation-renal cell carcinoma and institutional confirmation of either robust TFE3 nuclear protein expression by immunohistochemistry or evidence of TFE3 or TFEb translocation by either FISH or RT-PCR in a CLIA-certified laboratory. **Sites are required to submit tumor samples within 4 weeks of initiating protocol therapy, and are encouraged to submit tumor samples at second look surgery, relapse, or autopsy.** All reviews are retrospective and results from the reviews will not be returned to the submitting institution.

14.2.1 Suggested Minimal Histologic Sampling

14.2.1.1 Incisional Biopsy Material

If practical, all tissues should be processed. Needle biopsy specimens are the least desirable for classification of primary tumors. If needle biopsies are obtained, it is helpful to divide the tissue in multiple cassettes (1-2 cores per cassette) for optimum conservation of tissue.

14.2.1.2 Tumor Excision/Nephrectomy

Representative tissue blocks are needed from various regions of the mass for tumor classification. Adequate sampling requires approximately 1 section per cm diameter of tumor. The narrowest tissue margins should be sampled to adequately assess the surgical margins. Sections demonstrating the relationship between the tumor and the renal sinus, renal capsule, as well as the adjacent kidney are most useful.

14.3 Pathology Review Submission Checklist

Please send the following items for the retrospective pathology review:

- A complete set of recut H&E slides to be retained by the review pathologists.
- A representative formalin-fixed paraffin block of tumor material (paraffin blocks will be returned after sectioning upon request only). **NOTE:** If blocks cannot be sent on a permanent basis, then send 10 plus-charged (polarized) unstained sections (4 micron section thickness) for immunoperoxidase and other special studies from 1-2 representative blocks of tumor tissue.
- Documentation including:
  - Institutional Final Pathology Report
  - Pathology Checklist
  - Institutional Cytogenetics/Molecular Pathology Report (if available)
  - Institutional Operative Report
  - AREN1721 Specimen Transmittal Form

14.4 Shipping

Label all materials with the patient's COG patient identification number. Blocks or slides for central review must also be labeled with the surgical pathology ID and block number from the corresponding pathology report.

Send all pathology central review materials via regular mail or using the institution's courier account to:

Biopathology Center
Nationwide Children's Hospital
700 Children's Drive WA1340
Columbus, OH 43205
Phone: (614) 722-2865
Fax: (614) 722-2897
Email: BPCParaffinTeam@nationwidechildrens.org

14.4.1 Study Pathologists

The BPC will send pathology review materials for retrospective central review to the study pathologist, Elizabeth J. Perlman, MD, at Ann & Robert H. Lurie Children's Hospital of Chicago.

14.5 Consultation

If a consultation for a difficult case is desired, this would be on a consultation-only basis and a fee may be charged. If a consultation is desired, the institution should contact the pathologist directly to request a consultation. Consultation materials (all slides, a block or unstained slides, and surgical pathology report) should be shipped using your own courier account to the study review pathologist listed below.

Elizabeth J. Perlman, MD
Ann & Robert H. Lurie Children's Hospital of Chicago
225 E. Chicago Ave. 08-423
Chicago, IL 60611
Phone: (312) 227-3967
Email: eperlman@luriechildrens.org

Please note: materials sent to a reviewer for consultation are separate from study submission.

15.0 SPECIAL STUDIES SPECIMEN REQUIREMENTS

15.1 Required Pharmacokinetics

As of Amendment 5A, all pediatric patients enrolled and randomized to Arm A or those who cross-over from Arm C to Arm A are required to provide specimens for PK testing. Please refer to the PK lab manual posted on the protocol webpage for details on ordering a PK sample collection kit. PK kits are **not** provided by the BPC.

NOTE: A kit should be ordered when a reservation is made for a potential pediatric enrollment on the study.

15.1.1 Required population for PK studies

For pediatric patients (age: ≥ 12 months to < 18 years) enrolled and randomized to Arm A (axitinib + nivolumab) or those who cross-over from Arm C to Arm A, sites will be required to collect and submit PK specimens. PK analysis will be conducted at a centralized laboratory.

15.1.2 Sample Collection and Handling Instructions

Patients should be instructed to hold the morning axitinib dose on Day 1 of Cycles 2 and 3 until after the pre-dose PK has been drawn.

Prior to collection of blood, wrap 2-mL K_3-EDTA tubes completely in aluminum foil to protect the samples from light.

NOTE: The samples for PK can be drawn from a central line, including a central line used to administer study drug.

Blood samples (2 mL per sample) will be collected into aluminum foil covered 2-mL tubes containing K_3-EDTA anticoagulant at the time points listed below:

For patients randomized to Arm A:

- Cycle 1, Day 1: at 2, 4, and 6 hours after AM dose of axitinib
- Cycle 2, Day 1: Pre-dose of axitinib
- Cycle 3, Day 1: Pre-dose of axitinib

For patients initially on Arm C who cross-over to Arm A at disease progression:

- The day that the first dose of axitinib is given: at 2, 4, and 6 hours after AM dose

- Cycle 2, Day 1 of combination therapy: Pre-dose of axitinib
- Cycle 3, Day 1 of combination therapy: Pre-dose of axitinib

NOTE: The first cycle of combination therapy after cross-over will be defined as the cycle for which > 14 days of axitinib is given, with Day 1 of Cycle 1 after cross-over defined as the day of first nivolumab dose during that cycle after axitinib is started or on the day axitinib is started if given concurrently.

Special precautions should be taken to minimize the exposure to light of the PK blood and plasma specimens to avoid rapid degradation of axitinib .

Samples should be kept in an ice bath (do not submerge the tubes) until processing. Record the exact time the sample is collected along with the exact time the drug is administered in the Pharmacokinetic Sample Requisition Form. This requisition form will be provided in the PK sample collection kit.

The samples must be processed **immediately** at 2 °C to 8 °C .

15.1.3 Sample Processing

1. Fill 2-mL K_3-EDTA collection tube(s) completely.
2. Mix immediately by gently inverting the tube(s) at least 8 to 10 times and place in an ice bath (do not submerge) until centrifugation.
3. Centrifuge at 2°C to 8°C at approximately 1700 x g for at least 10 minutes until cells and plasma are well separated.
4. Use a pipette to transfer all the plasma into the appropriately labeled amber tube. Use a different pipette to aliquot plasma for each PK sample collected to avoid cross-contamination between time points.
5. All samples should be stored in an opaque box to protect from light exposure. **Any sample inadvertently exposed to light for 5 minutes or more should be flagged (with an asterisk) for possibly spurious results**. On the Pharmacokinetic Sample Requisition Form indicate whether the sample was exposed to light for ≥ 5 minutes.
6. Freeze at -70 °C within 1 hour of collection and store frozen in a freezer with no defrost cycle until shipment.

15.1.4 Sample Labeling and Shipping Instructions

Please refer to the PK lab manual posted on the protocol webpage for complete sample labeling and shipping instructions. **NOTE**: PK samples are to be shipped to a central lab. Do **NOT** ship to the BPC.

Any sample exposed to light for ≥ 5 minutes should be marked with an asterisk. Data should be recorded on the Pharmacokinetic Sample Requisition Form, which must accompany the sample(s).

Samples should be batched per patient and shipped frozen on dry ice in opaque containers at the end of each cycle.

15.1.5 Methodology

Plasma concentrations of axitinib will be determined at a centralized laboratory using validated assays.

Concentrations for axitinib will be plotted for each cohort using a box-whisker plot by time, day, and cycle.

15.2 Optional Studies

If limited specimens are available, specimens for correlative biology studies (Sections 15.2.1 and 15.2.2) should be prioritized, followed by specimens for banking (Section 15.2.3).

15.2.1 Immunotherapy Biomarkers in Blood

15.2.1.1 Specimens

In consenting patients, peripheral blood will be acquired (15-20 mL per sample) in green top sodium tubes at the following timepoints:

- Before treatment initiation
- Before Day 1 of Cycles 2, 3, and 9 (within 72 hours prior to Day 1 dosing)
- Within 3 weeks after the last dose of study treatment

Lithium heparin tubes are also acceptable if a site is unable or unwilling to obtain green top sodium tubes due to cost or availability.

15.2.1.2 Sample Processing

Blood samples should be sent as whole blood at room temperature.

15.2.1.3 Labeling

Using a waterproof marker, label the tubes with the following: COG study number, patient ID, date and timepoint of specimen drawn.

15.2.1.4 Shipping

Samples must be received in the laboratory within 24 hours of being drawn. Plan the draw and shipping accordingly. Blood samples should be shipped Monday through Thursday by Priority Overnight for delivery Tuesday through Friday. Deliveries will not be accepted on Saturdays or holidays. Please contact the lab before specimens are shipped.

Blood samples should be shipped to:

Cincinnati Children's Hospital Medical Center
Davies Lab C/O Kelly Lake, Rm. R2543
3333 Burnet Ave.
Cincinnati, OH 45229-3039

For the shipping account number and general questions, contact Kelly Lake at Kelly.Lake2@cchmc.org or (513) 636-3425.

15.2.1.5 Methodology

This study will assess biomarkers of clinical benefit when tRCC patients receive anti-VEGF and anti-PD1/PD-L1 based therapies. Immunologic evaluations will include PD-L1 expression, type of antitumor immune response and stability of T cell activation before and after treatment.

Peripheral blood mononuclear cell (PBMC) will be assessed for composition of CD4 and CD8 T cells, naïve and memory cells (CD54RO/RA, CCR7), recently activated T cells (HLADR, CD38, Nurr77, Ki67, the frequency of T cells with an exhausted phenotype (PD-1, Lag-3, Tim3, CD244), and regulatory phenotype (CD25, FoxP3). PBMC will also be assessed for Ca^{2+} influx capacity.

PBMC Isolation:
Immediately upon receipt of blood specimen, the laboratory will isolate the PBMCs via the Ficoll method. This isolation includes lysing the red blood cells (RBCs) and re-suspending the PBMCs in cryopreservation media with a minimum concentration of 1 million (1e6) cells/mL. These cells will be viably frozen and stored for future analysis. Additional samples including plasma may be stored from the blood specimen.

PBMCs will be thawed, spun down, re-suspended in PBS, and immediately plated into a 96 well U bottom plate. Cells will be incubated at 4˚C for 10 minutes in 1 µg/mL PBS Keytruda. After 10 minutes, cells will be washed with PBS and then labeled with manufacturer suggested amounts of Live dead eFluor 780 (e-bioscience), anti-CD8 BV785, anti-CD4 AF488, RA PerCP, RO BV510, anti-CD25 BV660, IgG FC PE, anti-CD244 Pacific Blue (BioLegend), and HLA-DR Dylight350 (Novus Biologicals). Once labeled cells will be washed and re-suspended in FoxP3 Fixation/Permeabilization solution (e-bioscience). After cells are fixed, they will be labeled with Foxp3 AF647 (BioLegend) in Permeabilization buffer (e-bioscience). The cells are then washed with Permeabilization buffer and re-suspended in 1% formaldehyde in PBS. Cells are stored in the dark at 4˚C until acquisition on BD LSRFortessa flow cytometer.

15.2.2 Immunotherapy Biomarkers in Tissue
Tissues will be used to assess PD-L1 expression and TIL composition/distribution before treatment using multicolor imaging.

15.2.2.1 Specimens
In consenting patients, tumor tissue samples should be acquired before treatment initiation and on protocol therapy only if tissue is obtained for any clinical reason (i.e., surgery, relapse/progression, etc.). Tissue samples will be acquired fresh in 100 mg pieces. Tumor tissue for Immunotherapy Biomarkers should be stored fresh in sterile tissue culture media and refrigerated (6-8°C) until fixation, if immediate fixation is not possible. The length of time that tissue is stored in media prior to fixation should be noted in the AREN1721 Optional Studies specimen transmittal form.

15.2.2.2 Sample Processing
Tumor tissue should be fixed in 10% buffered formalin only (no other fixatives acceptable) for not less than 6 hours and no more than 5 days before alcohol-xylene-paraffin dehydration, paraffinization and subsequent embedding using established/automated processing

protocols for the appropriate size of tissue fragments. Sections cut from the prepared formalin fixed paraffin embedded blocks may be submitted, cut 4-5 microns thick, and placed on unstained, charged, and unbaked slides (10 total). Alternatively, a paraffin block can be substituted for slides.

15.2.2.3 Labeling

Using a waterproof marker, label the slides with the following: COG patient ID, BPC number, date of collection, surgical pathology ID, and block number from the corresponding pathology report.

15.2.2.4 Shipping

Tumor tissue slides or blocks (preferred), and the corresponding institutional pathology report, should be shipped by regular mail in a padded envelop or box along with a printed copy of the completed AREN1721 Optional Studies Specimen Transmittal form. Slides must be placed in a hard-sided plastic slide holder and wrapped in bubble wrap prior to shipment. During warm months, ship paraffin block(s) with a cold pack. Ship to the BPC:

Biopathology Center
Nationwide Children's Hospital
Protocol AREN1721
700 Children's Drive, Room WA1340*
Columbus, OH 43205

Phone: (614) 722-2865
Fax: (614) 722-2897
Email: BPCBank@nationwidechildrens.org

*The room number is required. Packages not listing the room number will be denied and returned to the sender.

15.2.2.5 Specimen Handling by Biopathology Center

Tissue specimens submitted as paraffin blocks will be sectioned by the BPC. The BPC will ship slides for immunotherapy biomarker testing to the Study Chair, James Geller, MD, at Cincinnati Children's Hospital Medical Center.

15.2.2.6 Methodology

Immunohistochemical Stains:
Preparation:
Formalin-fixed, paraffin-embedded tissues are suitable for use with Ventana ultraView Universal DAB detection kit and BenchMark, BenchMark XT, and BenchMark ULTRA instruments. Tissue sections are baked/heated for at least 2 hours (but not longer than 24 hours) in a 60° ± 5° C oven.

Immunostaining:
Immunostain clones include: Ventana/Roche: PD-L1 (SP263) rabbit monoclonal; CD3 (2GV6) rabbit; CD4 (SP35) rabbit; and CD8 (SP57) rabbit; and Cell Marque PD-1 (NAT105) mouse monoclonal. Preprogrammed protocols on Ventana BenchMark, BenchMark XT, and BenchMark ULTRA are performed for each specific antibody (CD3 2GV6 rabbit; CD4 SP35 rabbit; CD8 SP57 rabbit; PD-1 NAT105; PD-L1 SP 142). Following completion of the automated stain protocols, the slides will be removed from the stainers for post-instrument procedures.

Post-instrument procedures:
Slides are then washed with mild dishwashing detergent to remove coverslip solutions. Slides are then rinsed in distilled water to remove detergent. Slides are then dehydrated, cleared, and coverslipped with routine permanent mounting media. Slides are then submitted for interpretation by the pathologist.

15.2.3 Specimens for Banking

15.2.3.1 Specimens

In consenting patients, the following samples are requested. Blood and urine specimens are still requested if tissue is not available.

SPECIMEN	TIMEPOINT
Snap Frozen Tumor Tissue from primary tumor • At least 1 gram and up to 10 grams if available, in 1 gram aliquots	• At diagnosis prior to any chemotherapy • At any surgery while on study
Snap Frozen Normal Kidney Tissue • At least 1 gram and up to 10 grams if available, in 1 gram aliquots	• When available
Snap Frozen Tumor Tissue from biopsied metastatic areas (if obtained in addition to primary diagnostic site) • At least 1 gram and up to 10 grams if available, in 1 gram aliquots	• At diagnosis prior to any chemotherapy • At any surgery while on study
Formalin Fixed Block	• At diagnosis prior to any chemotherapy • At any surgery while on study
Whole Blood • 5-10 mL in EDTA tube	• Prior to any chemotherapy*
Serum • Spun from 6 mL of whole blood in red top tube	• Prior to any chemotherapy*
Urine • 5-10 mL	• Prior to any chemotherapy*

*Although pre-treatment specimens are **strongly preferred**, specimens collected after starting chemotherapy are acceptable if a pre-treatment sample cannot be collected.

15.1.3.2 Specimen Procurement Kits

Specimen procurement kits are provided to sites in North America by the BPC. To request a dual chamber specimen procurement kit, access the Kit Management system (https://ricapps.nationwidechildrens.org/KitManagement/) and select AREN1721 for the protocol.

The kits include foil for frozen tissue, plastic zip-lock baggies, and vials for frozen sera and urine. Also included with each kit are instructions, a dry ice label, Exempt Human Specimen sticker and 2 sets of secondary shipping envelopes with absorbent material.

15.1.3.3 Sample Processing and Labeling

Operating Room personnel should not put the tissue into fixative. The specimen should be brought to the Pathology Department quickly (by special messenger if necessary). It may be appropriate to hold occasional meetings of surgical, laboratory, and clinical personnel to emphasize the urgency of processing these specimens rapidly, preferably within 20 minutes.

Tissues should be as sterile as possible. After the necessary tissues are obtained for local institutional diagnosis, the remaining tissue should be submitted.

Specimens should be prepared promptly after collection as described below.

Snap Frozen Tissue:

Cut at least 1 specimen from the primary tumor or biopsy, and from metastatic areas (if resected or biopsied) into 1 gram (maximum) aliquots. Up to ten 1 gram aliquots may be submitted, if available. Wrap tissue in foil and snap freeze in vapor phase liquid nitrogen (do not submerge in liquid nitrogen) or cold isopentane. For biopsies which are less than 1 gram, please submit as much as possible. Foil and plastic baggies will be provided in the specimen procurement kit for the snap frozen tissue samples. Place a label inside each baggie stating the COG Patient ID Number, BPC number, specimen type (primary or metastatic), and collection date. If available, submit **normal kidney tissue** in addition to the tumor tissue. Each tissue type (primary, metastatic or normal) must be placed in separate baggies.

Formalin Fixed Block:

Submit formalin fixed tissue block(s) from representative primary, metastatic and normal tissue if available. The block must be labeled with the COG Patient ID number and the surgical pathology ID and block number from the corresponding pathology report. Primary, metastatic and normal tissue must be placed in separate bags and labeled appropriately.

Whole Blood:
Prior to any chemotherapy, collect 5-10 mL of whole blood, anticoagulated with EDTA (purple top tubes which are not provided in the specimen procurement kit) and keep at room temperature. Using a waterproof marker, label the tubes with the COG Patient ID Number, BPC number, specimen type (blood), and the collection date. If a specimen cannot be shipped the same day it is collected, please store at 4° C (refrigerator) and ship on the next working day. Although sampling prior to chemotherapy is strongly preferred, blood samples may be collected after the first dose of chemotherapy is administered.

Serum:
Prior to any chemotherapy, collect 6 mL of blood in a red top tube (which is not provided in the specimen procurement kit). Allow the blood to clot at 4°C (or in a bucket with ice) for at least 30 minutes. Spin at 1000g for 15 minutes at 4ºC (preferred) or room temperature to separate the serum. Transfer the serum into the cryovials provided in the specimen procurement kit and cap the tubes securely. Place a minimum of 0.25 mL into each cryovial. Due to protein degradation, the specimen should be processed and frozen within 2 hours of the blood collection. Using a waterproof marker, label the tubes with the COG Patient ID Number, BPC number, specimen type (serum), and the collection date. Place the tubes in a baggie labeled "serum". Freeze serum in an upright position in a -80ºC freezer until shipment.

Urine:
Prior to any chemotherapy and nephrectomy (if applicable), 5-10 mL of urine (not required to be sterile) should be collected from the patient and then transferred into a 15 mL conical tube labeled with patient identifiers. If urine is not processed immediately, store at 4°C prior to processing.

Spin urine at 1000g (2000rpm) for 10 minutes at 4°C (preferred). Urine may be spun at room temperature if a refrigerated centrifuge is not available. Aliquot urine into the 5 cryovials provided. Avoid any pellet that may have been formed at the bottom of the conical tube. Place a minimum of 0.25mL into each cryovial. The cryovials should be labeled with the COG Patient ID Number, BPC number, specimen type (urine), and date collected. Immediately **freeze the urine in an upright position** in a -80°C freezer until ready to ship.

15.1.3.4 Shipping

The dual chamber specimen procurement kit is constructed to allow shipment of frozen (**on dry ice**) and ambient temperature tissues in the same container. **Dry ice may be placed in either compartment of the kit, but should not be put in both. Include an AREN1721 optional studies specimen transmittal form with each shipment and a pathology report (whenever tissue is submitted).**

1. Before specimens are placed into the dual chamber specimen procurement kit, they first need to be placed in three separate layers of packaging. Package the frozen specimens and the ambient specimens separately since they will be placed in separate compartments of the kit. Two sets of the biohazard and Tyvek diagnostic envelopes are provided in the kit for this purpose.
    a. Place the specimens in zip lock bags (one bag per specimen type/time point).
    b. Place the zip lock bags in a biohazard envelope with the absorbent material. Expel as much air as possible and seal the envelope.
    c. Place the biohazard envelope inside a Tyvek envelope. Expel as much air as possible and seal the envelope.
2. Frozen specimens should be placed in one of the kit compartments filled with dry ice. Layer the bottom of the compartment with dry ice until it is approximately one-third full. Place the frozen specimens on top of the dry ice. Cover the specimens with the dry ice until the compartment is almost completely full. Place the foam lid on top to insulate the specimens during shipment.
3. Ambient temperature specimens should be shipped in the other kit compartment at room temperature. Insulate ambient specimens with bubble wrap or similar material.
4. Place the transmittal form(s) and any other required paperwork inside the kit chamber with the ambient specimens.
5. Place a foam cover on top of each kit chamber to insulate the specimens during shipment.
6. Close the outer lid of the specimen procurement kit and secure with filament or other durable sealing tape.
7. Sites in North America may print a shipping label via the BPC Kit Management application and attach to the top of the kit. Please note that a shipping label is not provided when blocks or slides are shipped separately.
8. Complete the dry ice label (UN 1845). Place the dry ice and Exempt Human Specimen labels on the side of the kit.
9. Arrange for Federal Express pickup per your usual institutional procedure or by calling 1-800-238-5355.

Kits should be shipped to the BPC on Monday through Thursday for Tuesday through Friday delivery. Saturday delivery is only available for fresh blood. Please hold other specimens collected on a Friday and ship the following Monday. When shipping blood on a Friday, select “Yes” For Saturday Delivery when printing the shipping label.

If a specimen is obtained on a week-end or holiday, please hold it under appropriate conditions until the next business day.

Send the specimens to:

Biopathology Center
Nationwide Children's Hospital
Protocol AREN1721
700 Children's Drive, Room WA1340*
Columbus, OH 43205

Phone: (614) 722-2865
Fax: (614) 722-2897
Email: BPCBank@nationwidechildrens.org

*The room number is required. Packages not listing the room number will be denied and returned to the sender.

15.1.3.5 Use of Banked Specimens
Exploratory biomarker testing of banked specimens will not occur until an amendment to this treatment protocol (or separate correlative science protocol) is reviewed and approved in accordance with National Clinical Trials Network (NCTN) policies. Amendments to the protocol and/or proposals for use of banked tissue or blood samples will include the appropriate background, experimental plans with assay details, and a detailed statistical section. Samples for testing will not be released for testing until the appropriate NCI approvals have been obtained.

16.0 IMAGING STUDIES REQUIRED AND GUIDELINES FOR OBTAINING

Timing of protocol therapy administration, response assessment studies, and surgical interventions are based on schedules derived from the experimental design or on established standards of care. Minor unavoidable departures (up to 72 hours) from protocol directed therapy and/or disease evaluations (and up to 1 week for surgery) for valid clinical, patient and family logistical, or facility, procedure and/or anesthesia scheduling issues are acceptable (except where explicitly prohibited within the protocol).

16.1 Goals of Diagnostic Imaging
Routine diagnostic imaging will be performed during treatment and follow-up, and at the time of suspected tumor progression/recurrence to detect and characterize sites of disease involvement as well as response. Investigators are encouraged to use a consistent modality for follow-up scans.

16.2 Timing of Diagnostic Imaging
16.2.1 Required Imaging Time Points
To document tumor, CT and/or MRI will be performed for all treatment arms, including after cross-over from Arm C to Arm A, according to following schedule:

- Pre-treatment
- After Cycles 2, 4, 6, 9, 12, and then every 4 cycles thereafter*
- At 6-8 weeks (not less than 4 weeks) following initial documentation of objective response (per Section 10.2)
- At any time where progressive disease is suspected
- At the end of treatment

- At relapse
- Follow-up assessments

Note: Tumors will be evaluated using RECIST v1.1 criteria, with the exceptions described in Section 10.2.1 to account for possible "pseudoprogression".

* For patients who remain on protocol therapy despite increase in tumor size ≥ 20%, imaging to include target lesions must occur every cycle, per Section 10.2.1. For patients who cross-over from Arm C to Arm A at initial progression, the cycle number should restart for the purposes of imaging to 'Cycle 1'. The first cycle of combination therapy after cross-over will be defined as the cycle for which > 14 days of axitinib is given, with Day 1 of Cycle 1 after cross-over defined as the day of first nivolumab dose during that cycle after axitinib is started or on the day axitinib is started if given concurrently. **NOTE:** The total protocol therapy received on AREN1721 (whether delivered on Arm A, Arm C, or Arm C+A) is not to exceed 26 cycles or 2 years, whichever comes first.

16.3 Required Imaging Studies

16.3.1 CT or MRI of the abdomen and pelvis

CT and MRI guidelines are available on the COG Member site at: https://members.childrensoncologygroup.org/_files/reference/RefMaterial/DiagnosticImagingGuidelines_MRI&CT.pdf

CT of the abdomen and pelvis should be collimated to at most 5 mm slice thickness. IV contrast in the portal venous phase (usually around 50s post-injection) is required. Oral contrast is not necessary.

MRI of the abdomen and pelvis should include T1 and T2 weighted images pre-contrast and post-contrast dynamic T1-weighted images through the kidneys. Diffusion weighted images are strongly recommended. Recommended b values for diffusion weighted imaging are b 50, 500, 1000 mm/s^2. Post contrast T1 weighted images through the kidneys should be acquired dynamically in the arterial (~20s), portal venous (~50s) and delayed phase. **Note:** The same imaging parameters should be used at each evaluation.

16.3.2 CT of the chest

CT of the chest should have enhanced lung windows. IV contrast is encouraged at diagnosis to assess for possible mediastinal adenopathy. Slice thickness should be 5 mm or less.

17.0 RADIATION THERAPY GUIDELINES

No radiation therapy is planned for this study.

APPENDIX I: CTEP AND CTSU REGISTRATION PROCEDURES

INVESTIGATOR AND RESEARCH ASSOCIATE REGISTRATION WITH CTEP

Food and Drug Administration (FDA) regulations and National Cancer Institute (NCI) policy require all individuals contributing to NCI-sponsored trials to register and to renew their registration annually. To register, all individuals must obtain a Cancer Therapy Evaluation Program (CTEP) Identity and Access Management (IAM) account at https://ctepcore.nci.nih.gov/iam. 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 https://ctepcore.nci.nih.gov/rcr.

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 https://ctep.cancer.gov/investigatorResources/default.htm. For questions, please contact the RCR ***Help Desk*** by email at RCRHelpDesk@nih.gov.

CTSU REGISTRATION PROCEDURES

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

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 (https://www.ctsu.org) 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 *COG*, and protocol number (*insert study number*).
- 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.)

Protocol-Specific Requirements For Site Registration:

- IRB approval (For sites not participating via the NCI CIRB; local IRB documentation, an IRB-signed CTSU IRB Certification Form, Protocol of Human Subjects Assurance Identification/IRB Certification/Declaration of Exemption Form, or combination is accepted)

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 in 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.

Checking Your Site's Registration Status
Site 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.

Data Submission / Data Reporting
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 CTEP-IAM account; and
- Assigned a Rave role on the LPO or PO roster at the enrolling site of: 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 an Non-Physician Investigator (NPIVR) or Investigator (IVR); and
- Rave Read Only role must have at a minimum an Associates (A) registration type.

Refer to https://ctep.cancer.gov/investigatorResources/default.htm for registration types and documentation required.

Rave-CTEP-AERS Integration
The Rave 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. 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 made to CTEP by telephone at 301-897-7497. Once internet connectivity is restored, the 24-hour notification that was phoned in must be entered immediately into CTEP-AERS using the direct 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 & Help Topics.

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

- NCI Guidelines for Investigators: Adverse Event Reporting Requirements is available at https://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/aeguidelines.pdf

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 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.

APPENDIX II: PERFORMANCE STATUS SCALES/SCORES

Performance Status Criteria Karnofsky and Lansky performance scores are intended to be multiples of 10					
ECOG (Zubrod)		**Karnofsky**		**Lansky***	
Score	Description	Score	Description	Score	Description
0	Fully active, able to carry on all pre-disease performance without restriction.	100	Normal, no complaints, no evidence of disease	100	Fully active, normal.
		90	Able to carry on normal activity, minor signs or symptoms of disease.	90	Minor restrictions in physically strenuous activity.
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light housework, office work.	80	Normal activity with effort; some signs or symptoms of disease.	80	Active, but tires more quickly
		70	Cares for self, unable to carry on normal activity or do active work.	70	Both greater restriction of and less time spent in play activity.
2	Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours	60	Required occasional assistance, but is able to care for most of his/her needs.	60	Up and around, but minimal active play; keeps busy with quieter activities.
		50	Requires considerable assistance and frequent medical care.	50	Gets dressed, but lies around much of the day; no active play, able to participate in all quiet play and activities.
3	Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.	40	Disabled, requires special care and assistance.	40	Mostly in bed; participates in quiet activities.
		30	Severely disabled, hospitalization indicated. Death not imminent.	30	In bed; needs assistance even for quiet play.
4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.	20	Very sick, hospitalization indicated. Death not imminent.	20	Often sleeping; play entirely limited to very passive activities.
		10	Moribund, fatal processes progressing rapidly.	10	No play; does not get out of bed.

*The conversion of the Lansky to ECOG scales is intended for NCI reporting purposes only.

APPENDIX III: BLOOD PRESSURE FOR PATIENTS < 18 YEARS OLD BY AGE AND HEIGHT

Blood pressure (BP) levels for BOYS

		Systolic Blood Pressure, mm Hg							Diastolic Blood Pressure, mm Hg						
Age	BP	Percentile of Height							Percentile of Height						
(years)	Percentile	5th	10th	25th	50th	75th	90th	95th	5th	10th	25th	50th	75th	90th	95th
1	95th	98	99	101	103	104	106	106	54	54	55	56	57	58	58
2	95th	101	102	104	106	108	109	110	59	59	60	61	62	63	63
3	95th	104	105	107	109	110	112	113	63	63	64	65	66	67	67
4	95th	106	107	109	111	112	114	115	66	67	68	69	70	71	71
5	95th	108	109	110	112	114	115	116	69	70	71	72	73	74	74
6	95th	109	110	112	114	115	117	117	72	72	73	74	75	76	76
7	95th	110	111	113	115	117	118	119	74	74	75	76	77	78	78
8	95th	111	112	114	116	118	119	120	75	76	77	78	79	79	80
9	95th	113	114	116	118	119	121	121	76	77	78	79	80	81	81
10	95th	115	116	117	119	121	122	123	77	78	79	80	81	81	82
11	95th	117	118	119	121	123	124	125	78	78	79	80	81	82	82
12	95th	119	120	122	123	125	127	127	78	79	80	81	82	82	83
13	95th	121	122	124	126	128	129	130	79	79	80	81	82	83	83
14	95th	124	125	127	128	130	132	132	80	80	81	82	83	84	84
15	95th	126	127	129	131	133	134	135	81	81	82	83	84	85	85
16	95th	129	130	132	134	135	137	137	82	83	83	84	85	86	87
≥17	95th	131	132	134	136	138	139	140	84	85	86	87	87	88	89

Instructions for using this BP Chart:

1. Measure the patient's blood pressure using an appropriate size cuff.
2. Select appropriate chart for a female or male patient.
3. Using the "age" row and "height" column to determine if the BP is within the ULN.
4. See Section 5.1.2.9 for definition of dose limiting hypertension, Section 5.2.5 for management and grading of hypertension, and Section 4.2.8 for medical treatment of axitinib related hypertension.

This table was taken from "The Fourth Report on the Diagnosis, Evaluation, and Treatment of High Blood Pressure in Children and Adolescents" PEDIATRICS Vol. 114 No. 2 August 2004, pp. 555-576.

Blood pressure (BP) levels for GIRLS

		Systolic Blood Pressure, mm Hg							Diastolic Blood Pressure, mm Hg						
Age	BP	Percentile of Height							Percentile of Height						
(years)	Percentile	5th	10th	25th	50th	75th	90th	95th	5th	10th	25th	50th	75th	90th	95th
1	95th	100	101	102	104	105	106	107	56	57	57	58	59	59	60
2	95th	102	103	104	105	107	108	109	61	62	62	63	64	65	65
3	95th	104	104	105	107	108	109	110	65	66	66	67	68	68	69
4	95th	105	106	107	108	110	111	112	68	68	69	70	71	71	72
5	95th	107	107	108	110	111	112	113	70	71	71	72	73	73	74
6	95th	108	109	110	111	113	114	115	72	72	73	74	74	75	76
7	95th	110	111	112	113	115	116	116	73	74	74	75	76	76	77
8	95th	112	112	114	115	116	118	118	75	75	75	76	77	78	78
9	95th	114	114	115	117	118	119	120	76	76	76	77	78	79	79
10	95th	116	116	117	119	120	121	122	77	77	77	78	79	80	80
11	95th	118	118	119	121	122	123	124	78	78	78	79	80	81	81
12	95th	119	120	121	123	124	125	126	79	79	79	80	81	82	82
13	95th	121	122	123	124	126	127	128	80	80	80	81	82	83	83
14	95th	123	123	125	126	127	129	129	81	81	81	82	83	84	84
15	95th	124	125	126	127	129	130	131	82	82	82	83	84	85	85
16	95th	125	126	127	128	130	131	132	82	82	83	84	85	85	86
≥17	95th	125	126	127	129	130	131	132	82	83	83	84	85	85	86

Instructions for using this BP Chart:

1. Measure the patient's blood pressure using an appropriate size cuff.
2. Select appropriate chart for a female or male patient.
3. Using the "age" row and "height" column to determine if the BP is within the ULN.
4. See Section 5.1.2.9 for definition of dose limiting hypertension, Section 5.2.5 for management and grading of hypertension, and Section 4.2.8 for medical treatment of axitinib related hypertension.

This table was taken from "The Fourth Report on the Diagnosis, Evaluation, and Treatment of High Blood Pressure in Children and Adolescents" PEDIATRICS Vol. 114 No. 2 August 2004, pp. 555-576.

APPENDIX IV: AXITINIB DOSING NOMOGRAMS FOR PATIENTS < 18 YEARS OLD

Axitinib Dose Level -1: 1.8 mg/m²/dose PO BID

BSA (m^2)	Total Daily Dose	AM Dose	PM Dose
0.53-0.69	2 mg	1 mg	1 mg
0.70-0.97	3 mg	2 mg	1 mg
0.98-1.35	4 mg	2 mg	2 mg
1.36-1.56	5 mg	3 mg	2 mg
1.57-1.97	6 mg	3 mg	3 mg
≥ 1.98	7 mg	4 mg	3 mg

Axitinib Dose Level 1 (STARTING DOSE): 2.4 mg/m²/dose PO BID

BSA (m^2)	Total Daily Dose	AM Dose	PM Dose
0.53-0.69	3 mg	2 mg	1 mg
0.70-0.93	4 mg	2 mg	2 mg
0.94-1.14	5 mg	3 mg	2 mg
1.15-1.35	6 mg	3 mg	3 mg
1.36-1.56	7 mg	4 mg	3 mg
1.57-1.77	8 mg	4 mg	4 mg
1.78-1.97	9 mg	5 mg	4 mg
≥ 1.98	10 mg	5 mg	5 mg

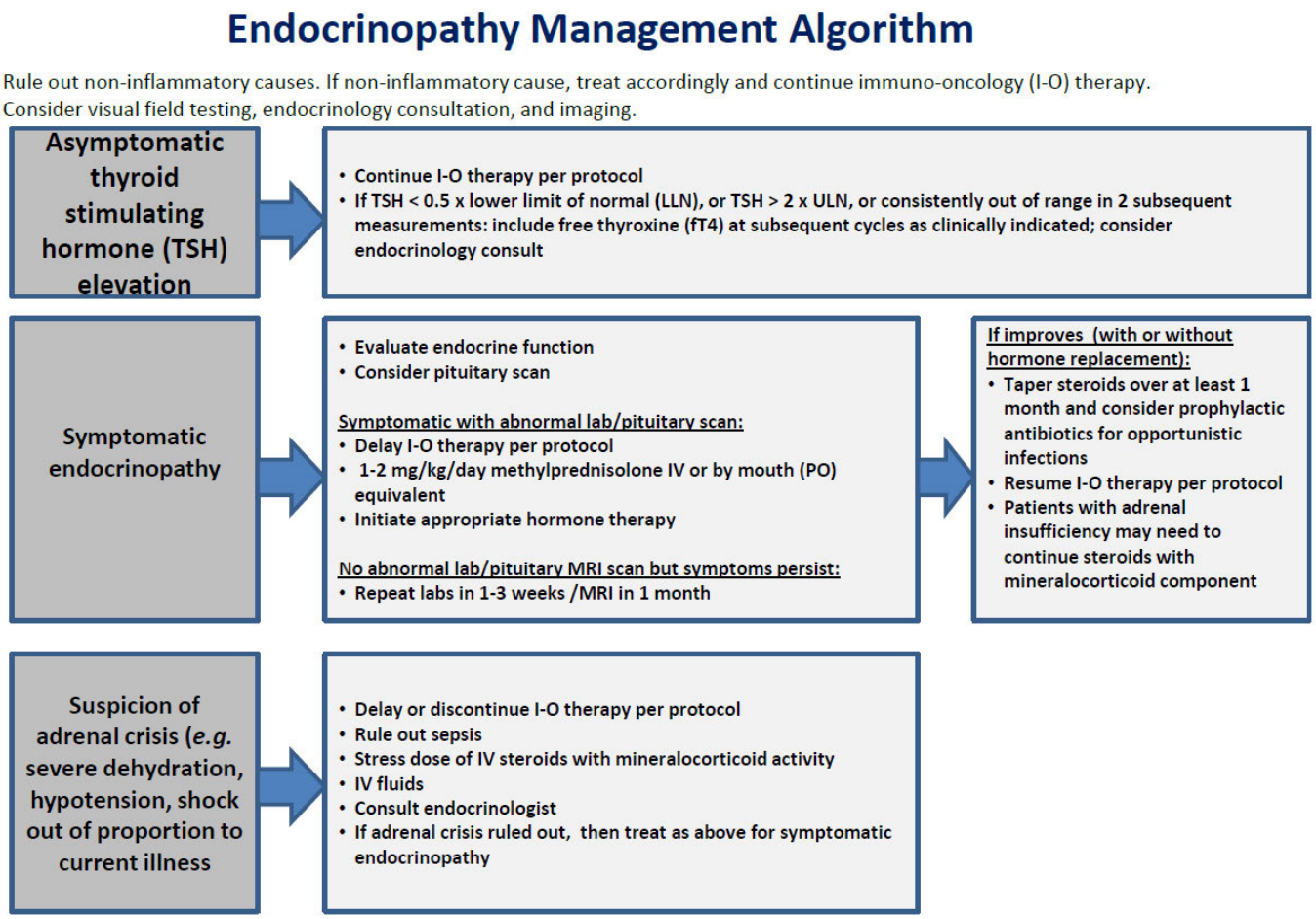
Axitinib Dose Level 2 (Dose Titration)

BSA (m^2)	Total Daily Dose	AM Dose	PM Dose
0.53-0.69	4 mg	2 mg	2 mg
0.70-0.93	5 mg	3 mg	2 mg
0.94-1.14	6 mg	3 mg	3 mg
1.15-1.35	8 mg	4 mg	4 mg
1.36-1.56	9 mg	5 mg	4 mg
1.57-1.77	10 mg	5 mg	5 mg
1.78-1.97	11 mg	6 mg	5 mg
≥ 1.98	12 mg	6 mg	6 mg

Axitinib Dose Level 3 (Dose Titration)

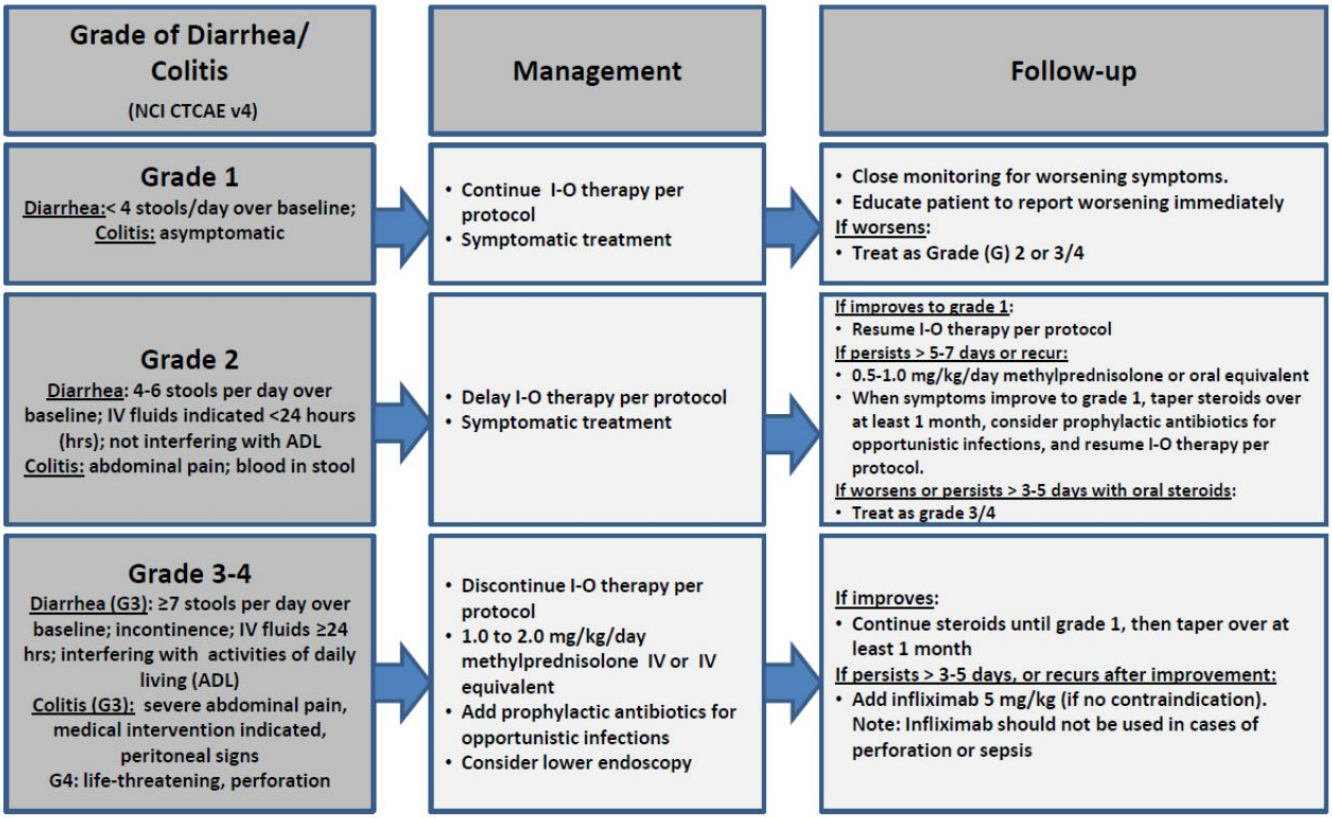
BSA (m^2)	Total Daily Dose	AM Dose	PM Dose
0.53-0.69	5 mg	3 mg	2 mg
0.70-0.93	6 mg	3 mg	3 mg
0.94-1.14	8 mg	4 mg	4 mg
1.15-1.35	10 mg	5 mg	5 mg
1.36-1.56	11 mg	6 mg	5 mg
1.57-1.77	12 mg	6 mg	6 mg
1.78-1.97	13 mg	7 mg	6 mg
≥ 1.98	14 mg	7 mg	7 mg

APPENDIX V: BRISTOL MYERS SQUIBB NIVOLUMAB TREATMENT GUIDELINES ALGORITHM



GI Adverse Event Management Algorithm

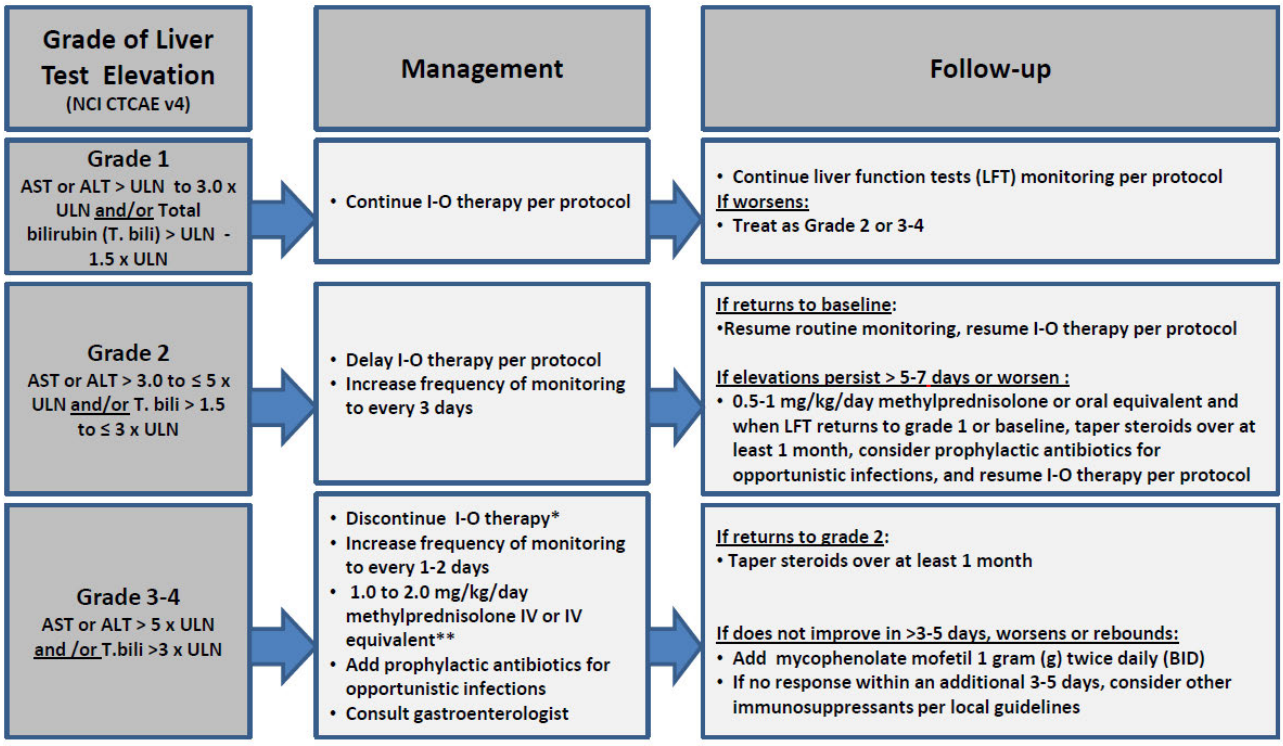
Rule out non-inflammatory causes. If non-inflammatory cause is identified, treat accordingly and continue I-O therapy. Opiates/narcotics may mask symptoms of perforation. Infliximab should not be used in cases of perforation or sepsis.



Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of oral corticosteroids.

Hepatic Adverse Event Management Algorithm

Rule out non-inflammatory causes. If non-inflammatory cause, treat accordingly and continue I-O therapy. Consider imaging for obstruction.



Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of oral corticosteroids.

***I-O therapy may be delayed rather than discontinued if AST/ALT ≤ 8 x ULN and T.bili ≤ 5 x ULN.**

****The recommended starting dose for grade 4 hepatitis is 2 mg/kg/day methylprednisolone IV.**

Note: The dosing of any medications above are provided for patients ≥ 18 years of age.

Neurological Adverse Event Management Algorithm

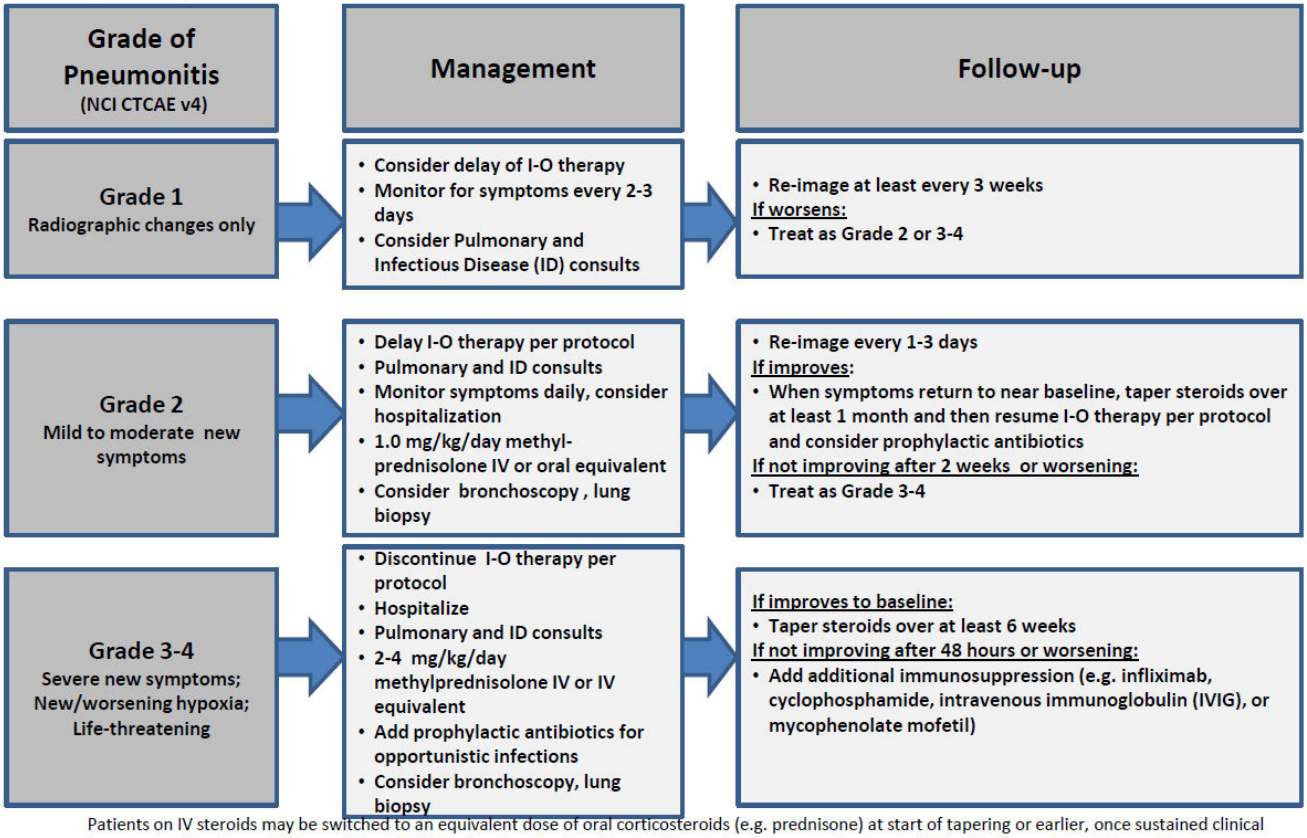
Rule out non-inflammatory causes. If non-inflammatory cause, treat accordingly and continue I-O therapy.

Grade of Neurological Toxicity (NCI CTCAE v4)	Management	Follow-up
Grade 1 Asymptomatic or mild symptoms; Intervention not indicated	• Continue I-O therapy per protocol	Continue to monitor the patient. If worsens: • Treat as Grade 2 or 3-4
Grade 2 Moderate symptoms; Limiting instrumental ADL	• Delay I-O therapy per protocol • Treat symptoms per local guidelines • Consider 0.5 to 1.0 mg/kg/day methylprednisolone IV or PO equivalent	If improves to baseline: •Resume I-O therapy per protocol when improved to baseline If worsens: • Treat as Grade 3-4
Grade 3-4 Severe symptoms; Limiting self-care ADL; Life-threatening	• Discontinue I-O therapy per protocol • Obtain neurology consult • Treat symptoms per local guidelines • 1.0-2.0 mg/kg/day IV methylprednisolone IV or IV equivalent • Add prophylactic antibiotics for opportunistic infections	If improves to Grade 2: • Taper steroids over at least 1 month If worsens or atypical presentation: • Consider IVIG or other immunosuppressive therapies per local guidelines

Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of oral corticosteroids.

Pulmonary Adverse Event Management Algorithm

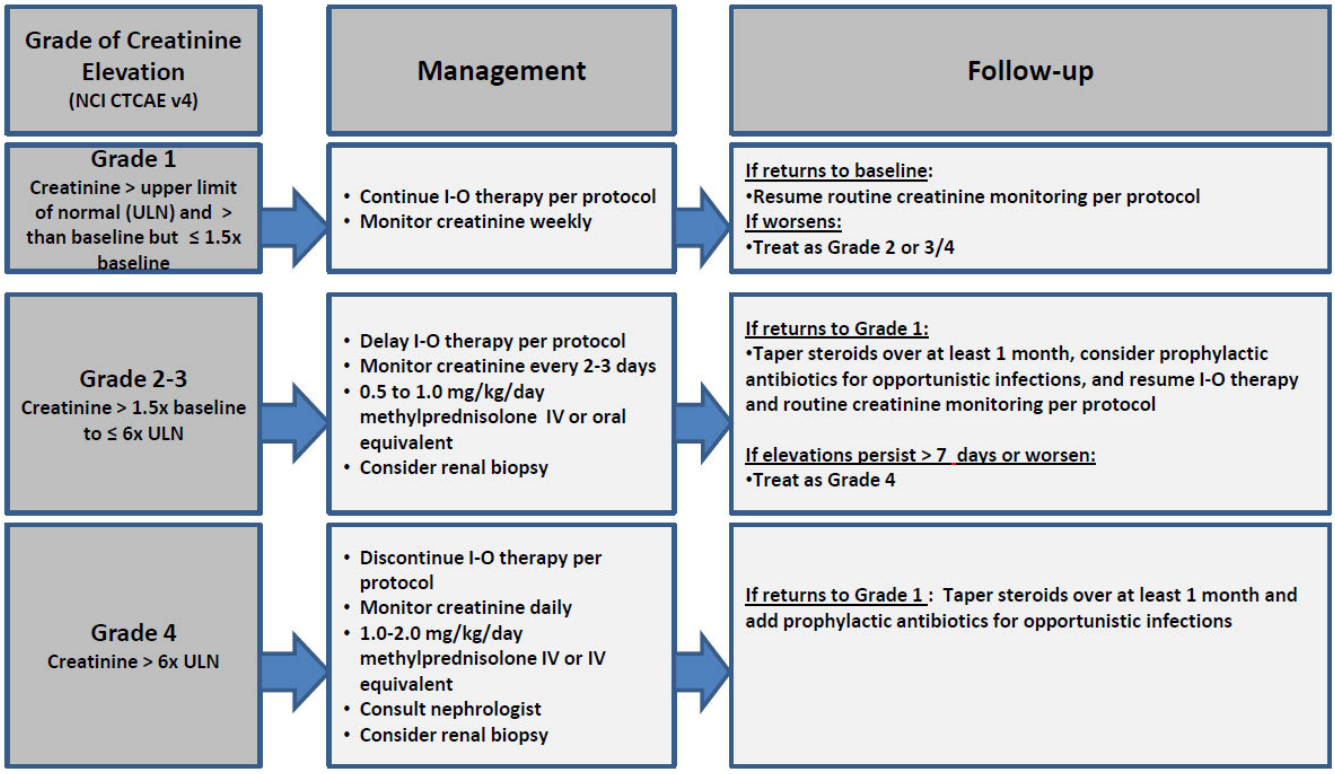
Rule out non-inflammatory causes. If non-inflammatory cause, treat accordingly and continue I-O therapy. Evaluate with imaging and pulmonary consultation.



Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of oral corticosteroids.

Renal Adverse Event Management Algorithm

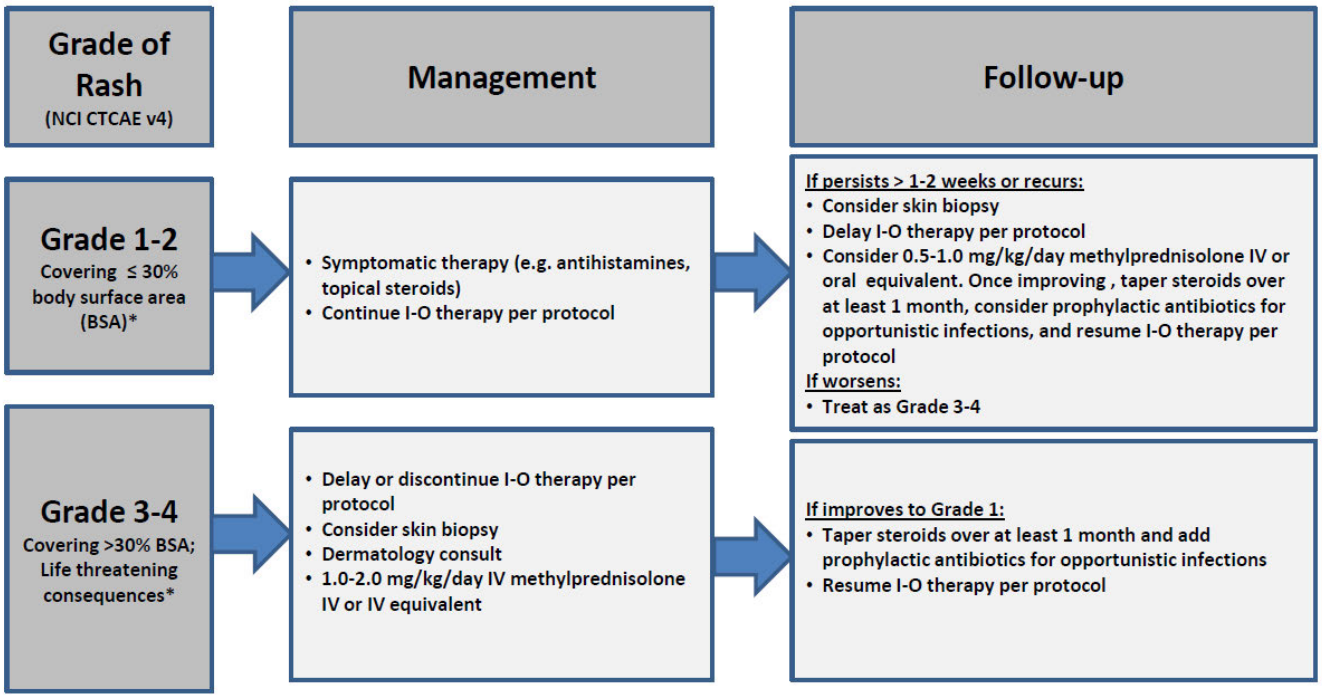
Rule out non-inflammatory causes. If non-inflammatory cause, treat accordingly and continue I-O therapy



Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of oral corticosteroids.

Skin Adverse Event Management Algorithm

Rule out non-inflammatory causes. If non-inflammatory cause, treat accordingly and continue I-O therapy.



Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of oral corticosteroids.
*Refer to NCI CTCAE v4 for term-specific grading criteria.

APPENDIX VI: CYP3A4 SUBSTRATES, INDUCERS, AND INHIBITORS

This is NOT an all-inclusive list. Because the lists of these agents are constantly changing, it is important to regularly consult frequently updated medical references.

CYP3A4 substrates	Strong Inhibitors[1]	Moderate Inhibitors	Strong Inducers	Moderate Inducers
abemaciclib acalabrutinib[5] alfentanil[4,5] alprazolam[5] amiodarone[4] amlodipine aprepitant/fosaprepitant atorvastatin avanafil[5] axitinib bortezomib bosutinib[5] brexpiprazole brigatinib budesonide[5] buspirone[5] cabozantinib calcium channel blockers cisapride citalopram/escitalopram cobimetinib[5] colchicine[5] conivaptan[5] copanlisib crizotinib cyclosporine[4] dabrafenib dapsone darifenacin[5] darunavir[5] dasatinib[5] dexamethasone[2] diazepam dihydroergotamine docetaxel doxorubicin dronedarone[5] ebastine[5] eletriptan[5] eliglustat[5] eplerenone[5] ergotamine[4] erlotinib estrogens etoposide	atazanavir boceprevir clarithromycin ceritinib cobicistat danoprevir/ritonavir darunavir delavirdine elvitegravir/ritonavir grapefruit[3] grapefruit juice[3] idelalisib indinavir/ritonavir itraconazole ketoconazole lopinavir/ritonavir nefazodone nelfinavir paritaprevir/ritonavir/ ombitasvir +/- dasabuvir posaconazole ritonavir saquinavir telaprevir telithromycin tipranavir/ritonavir tucatinib voriconazole	aprepitant conivaptan crizotinib diltiazem dronedarone duvelisib erythromycin fedratinib fluconazole fosamprenavir fosnetupitant grapefruit[3] grapefruit juice[3] imatinib isavuconazole lefamulin letermovir mifepristone netupitant nilotinib ribociclib verapamil	apalutamide barbiturates carbamazepine enzalutamide fosphenytoin lumacaftor/ ivacaftor mitotane phenobarbital phenytoin primidone rifampin St. John's wort	bosentan cenobamate dabrafenib efavirenz eslicarbazepine etravirine lorlatinib modafinil nafcillin pexidartinib rifabutin rifapentin

everolimus[5] felodipine[5] fentanyl[4] gefitinib haloperidol ibrutinib[5] idelalisib imatinib indinavir[5] irinotecan isavuconazole[5] itraconazole ivacaftor ketoconazole lansoprazole lapatinib lomitapide[5] lorlatinib losartan lovastatin[5] lurasidone[5] macrolide antibiotics maraviroc[5] medroxyprogesterone methadone midazolam[5] midostaurin[5] modafinil naloxegol[5] nefazodone nilotinib nisoldipine[5] olaparib ondansetron osimertinib paclitaxel palbociclib pazopanib pimozide[5] quetiapine[5] quinidine[4] regorafenib rilpivirine[5] rivaroxaban[5] romidepsin saquinavir[5] sildenafil[5] simvastatin[5] sirolimus[4,5] sonidegib sunitinib tacrolimus[4,5] tamoxifen				

tadalafil[5] telaprevir temsirolimus teniposide tetracycline ticagrelor[5] tipranavir[5] tolvaptan[5] triazolam[5] trimethoprim vardenafil[5] vemurafenib venetoclax[5] vinca alkaloids zolpidem				

[1] Certain fruits, fruit juices and herbal supplements (star fruit, Seville oranges, pomegranate, gingko, goldenseal) may inhibit CYP 3A4 isozyme, however, the degree of that inhibition is unknown.
[2] Refer to Section 4.2 regarding use of corticosteroids.
[3] The effect of grapefruit juice (strong vs moderate CYP3A4 inhibition) varies widely among brands and is concentration-, dose-, and preparation-dependent.
[4] Narrow therapeutic range substrates
[5] Sensitive substrates (drugs that demonstrate an increase in AUC of ≥5-fold with strong inhibitors)

APPENDIX VII: GLOMERULAR FILTRATION RATE (GFR) CALCULATIONS

Measurement of GFR should be undertaken at the recommended timepoints as indicated in the required observations. **GFR may be obtained via nuclear Tc99 method, 24 hour urine collection method, OR estimated using the formulas below.**

GFR tests should not be done when the patient is receiving IV hydration as the result will not be reliable. Repeat assessments should use the same technique, as per local practices.

Updated Schwartz's Formula (0-18 years)
According to new bedside Schwartz's formula,[75] GFR (eGFR) can be estimated from single serum samples:

$$\text{eGFR (mL/min/1.73m}^2\text{)} = 0.413 \times \text{height (cm)/Scr (mg/dL)}$$

- Normal 120
- Normal range 90-120

For adult patients (> 18 years of age)
The Modification of Diet in Renal Disease (MDRD) equation[76] should be used to calculate eGFR:

$$\text{eGFR (mL/min/1.73m}^2\text{)} = 175 \times (\text{Scr})^{-1.154} \times (\text{Age})^{-0.203} \times (0.742 \text{ if female}) \times (1.212 \text{ if African American})$$

PLEASE NOTE: These formulas have not been confirmed in patients receiving repeated cycles of intensive chemotherapy. GFR may be overestimated by these methods due to tubular section of creatinine.

APPENDIX VIII: YOUTH INFORMATION SHEETS

INFORMATION SHEET REGARDING RESEARCH STUDY AREN1721
(for children from 7 through 12 years of age)

A study to compare treatments for a type of kidney cancer called tRCC

1. We have been talking with you about your cancer. tRCC is a type of cancer that grows in the kidneys. After doing tests, we have found that you have this type of cancer.

2. We are asking you to take part in a research study because you have tRCC. A research study is when doctors work together to try out new ways to help people who are sick. At this time, there is no treatment that is typical for tRCC. In this study, we are trying to learn more about how to treat it by using 2 different drugs. We do not know how well these drugs will work in children, teens, and young adults with tRCC. That is why we are doing this study.

3. Children who are part of this study will be treated in 1 of 2 ways. You will get either the one drug by itself, or two drugs together. There is a 50:50 chance you will receive one drug or two-drug treatment. You will also have tests to see if the cancer is getting worse, staying the same, or getting better. If you have treatment with one drug and your cancer gets worse, then you may be able to switch to the two-drug treatment.

4. Sometimes good things can happen to people when they are in a research study. These good things are called “benefits.” We hope that a benefit to you of being part of this study is getting rid of the cancer for a long time, but we don’t know for sure if there is any benefit of being part of this study.

5. Sometimes bad things can happen to people when they are in a research study. These bad things are called “risks.” The risks to you from this study are that the study treatments may cause bad side effects. There is also the risk that the treatments may not work and that your cancer keeps growing. Other things may happen to you that we don’t yet know about.

6. Your family can choose to be part of this study or not. Your family can also decide to stop being in this study at any time once you start. There may be other treatments for your illness that your doctor can tell you about. Make sure to ask your doctors any questions that you have.

7. We are asking your permission to collect additional blood, urine and tumor samples. We want to see if there are ways to tell how the cancer will respond to treatment. These samples would be taken when other standard blood tests or surgery are being performed, so there would be no extra procedures. You can still take part in this study even if you don't allow us to collect the extra blood, urine or tumor samples for research.

INFORMATION SHEET REGARDING RESEARCH STUDY AREN1721
(for teens from 13 through 17 years of age)

A study to compare treatments for a type of kidney cancer called tRCC

1. We have been talking with you about your cancer. tRCC is a type of cancer that grows in the kidneys. After doing tests, we have found that you have this type of cancer.

2. We are asking you to take part in a research study because you have tRCC. A research study is when doctors work together to try out new ways to help people who are sick. At this time, there is no treatment that is typical for tRCC. In this study, we are trying to learn more about how to treat it by using 2 drugs called axitinib and nivolumab. We do not know how well these drugs will work in children, teens, and young adults with tRCC. That is why we are doing this study.

3. Children and teens who are part of this study will be treated in 1 of 2 ways. You will get either nivolumab by itself, or axitinib and nivolumab together. There is a 50:50 chance you will receive nivolumab by itself, or axitinib and nivolumab together. You will also have imaging tests to see if the cancer is getting worse, staying the same, or getting better. If you have treatment with nivolumab by itself and your cancer gets worse, then you may have the option to receive axitinib and nivolumab together.

4. Sometimes good things can happen to people when they are in a research study. These good things are called “benefits.” We hope that a benefit to you of being part of this study is getting rid of the cancer for a long time, but we don’t know for sure if there is any benefit of being part of this study.

5. Sometimes bad things can happen to people when they are in a research study. These bad things are called “risks.” The risks to you from this study are that the study treatments may cause bad side effects. There is also the risk that the treatments may not work and that your cancer keeps growing. Other things may happen to you that we don’t yet know about.

6. Your family can choose to be part of this study or not. Your family can also decide to stop being in this study at any time once you start. There may be other treatments for your illness that your doctor can tell you about. Make sure to ask your doctors any questions that you have.

7. We are asking your permission to collect additional blood, urine and tumor samples. We want to see if there are ways to tell how the cancer will respond to treatment. These samples would be taken when other standard blood tests or surgery are being performed, so there would be no extra procedures. You can still take part in this study even if you don't allow us to collect the extra blood, urine or tumor samples for research.

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