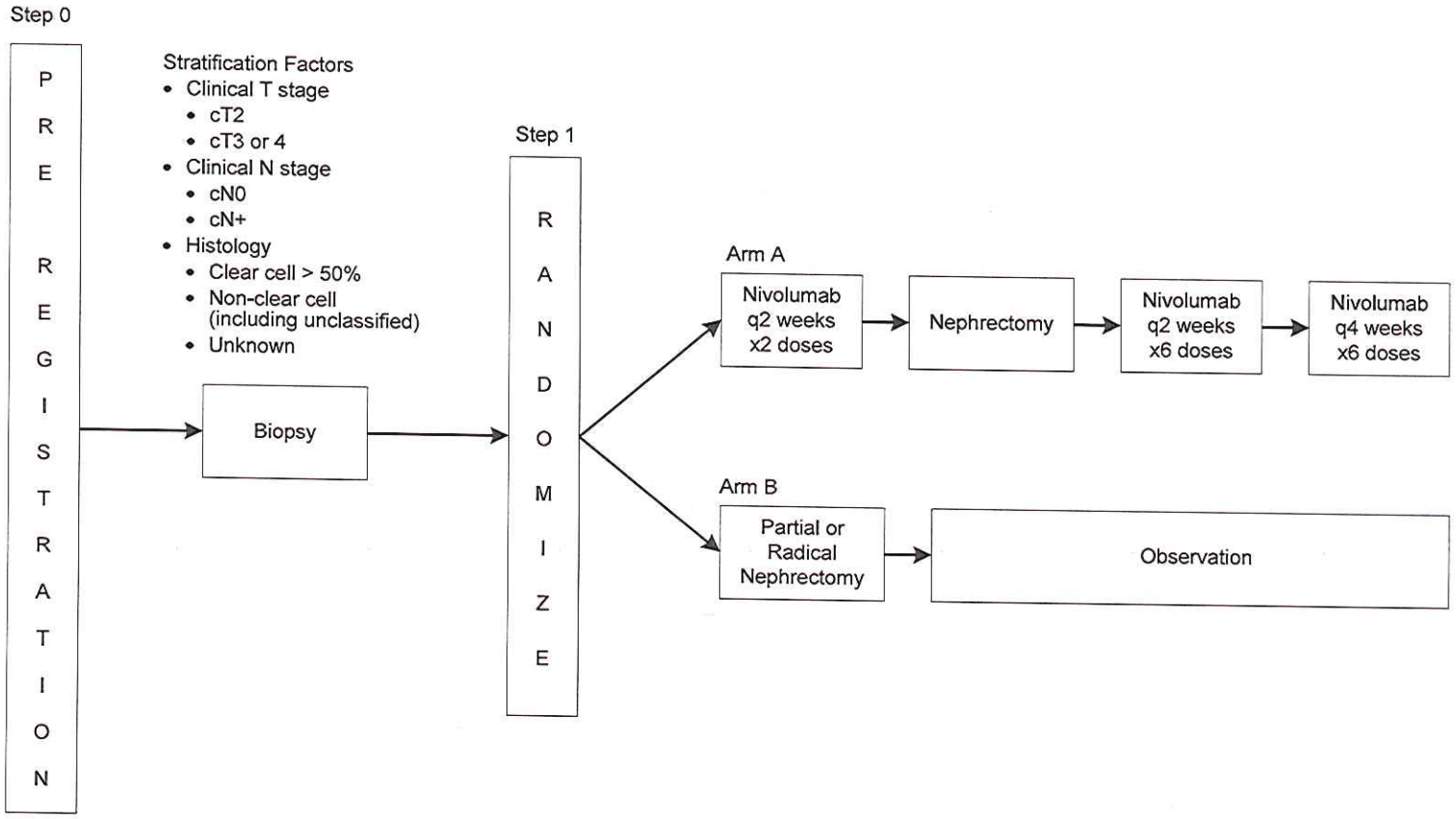
Schema



1. RCC must have been confirmed by biopsy within 4 months prior to randomization in order to avoid exposing patients to neoadjuvant nivolumab who clearly have a benign lesion or another type of cancer. If biopsy was not performed per standard of care patient is to be pre-registered and biopsy performed during step 0 to confirm RCC and eligibility.
2. After 115 patients with non-clear cell (including unclassified) or unknown histology have been enrolled, further accrual will be limited to patients with predominantly clear cell (> 50%) RCC

3. Selection of Patients

Each of the criteria in the checklist that follows must be met in order for a patient to be considered eligible for this study. Use the checklist to confirm a patient's eligibility. For each patient, this checklist must be photocopied, completed and maintained in the patient's chart.

In calculating days of tests and measurements, the day a test or measurement is done is considered Day 0. Therefore, if a test is done on a Monday, the Monday four weeks later would be considered Day 28.

ECOG-ACRIN Patient No. _____

Patient's Initials (L, F, M) _____

Physician Signature and Date _____

NOTE: CTEP Policy does not allow for the issuance of waivers to any protocol specified criteria (http://ctep.cancer.gov/protocolDevelopment/policies_deviations.htm). Therefore, all eligibility criteria listed in Section 3 must be met, without exception. The registration of individuals who do not meet all criteria listed in Section 3 can result in the participant being censored from the analysis of the study, and the citation of a major protocol violation during an audit. All questions regarding clarification of eligibility criteria must be directed to the Group's Executive Officer (EA.ExecOfficer@jimmy.harvard.edu) or the Group's Regulatory Officer (EA.RegOfficer@jimmy.harvard.edu).

NOTE: Institutions may use the eligibility checklist as source documentation if it has been reviewed, signed, and dated prior to registration/randomization by the treating physician.

NOTE: This study involves preregistration and randomization.

All patients must undergo biopsy in order to avoid exposing patients to neoadjuvant nivolumab who clearly have a benign lesion or another type of cancer. This can be a diagnostic biopsy occurring within 4 months prior to randomization or the research biopsy available to consenting patients after pre-registration to the study. If the biopsy clearly demonstrates a benign condition or a different type of cancer, the patient is not eligible to be randomized. All other outcomes, including results that are ambiguous or inconclusive, will be considered a good faith effort and the patient can be randomized to the treatment step

NOTE: **Subject Re-enrollment:** This study permits the re-enrollment of a subject that has discontinued the study as a screen failure (i.e., subject has not been randomized / has not been treated). If re-enrolled, the subject must be re-consented and meet the eligibility criteria detailed below.

3.1 Eligibility Criteria for Preregistration (Step 0)

3.1.1 Preoperative biopsy for confirmation of RCC must be performed within four (4) months prior to randomization.

If biopsy was performed as part of patients standard care, and will not be performed during Step 0 proceed directly to randomization.

NOTE: Refer to Section 10.5 for non-standard of care biopsy reimbursement guidelines.

3.2 Eligibility Criteria for Randomization (Step 1)

_____ 3.2.1 Patients with newly diagnosed higher risk RCC of any histology including sarcomatoid or (if preoperative biopsy was uninformative) – "unknown" histology. RCC must have been confirmed by biopsy within 4 months prior to randomization in order to avoid exposing patients to neoadjuvant nivolumab who clearly have a benign lesion or another type of cancer. If the biopsy clearly demonstrated a benign condition or a different type of cancer, the patient is not eligible to be randomized.

_____ 3.2.2 Clinical stage ≥ T2NxM0 disease or TanyN+ disease for which radical or partial nephrectomy is planned.

_____ 3.2.3 Patients must have no clinical or radiological evidence of distant metastases (M0)

_____ 3.2.4 No concurrent or prior systemic or local anti-cancer therapy for RCC is permitted. Examples of these prohibited therapies include:

_____ 3.2.4.1 Radical or partial nephrectomy for prior RCC

_____ 3.2.4.2 Metastectomy for RCC

_____ 3.2.4.3 Radiation therapy to the renal bed or any distant metastatic sites.

_____ 3.2.4.4 Antineoplastic systemic therapies for RCC: i.e., chemotherapy, hormonal therapy, immunotherapy, or standard or investigational agents for treatment of RCC

_____ 3.2.4.5 Prior treatment with an anti-PD-1, anti-PD-L1, anti-PD-L2, anti-CD137, or anti-CTLA-4 antibody, or any other antibody or drug specifically targeting T-cell co-stimulation or checkpoint pathways

NOTE: Please see Sections 5.2 and 5.3 for the lists of therapies that are prohibited and permitted for patients during treatment.

_____ 3.2.5 Age ≥ 18 years. Because no dosing or adverse event data are currently available on the use of nivolumab therapy in patients < 18 years of age, children are excluded from this study.

_____ 3.2.6 ECOG Performance Status: 0 or 1

_____ 3.2.7 Women must not be pregnant or breast-feeding, as the effects of nivolumab on the developing human fetus are unknown.

All females of childbearing potential must have a blood test or urine study within 2 weeks prior to registration to rule out pregnancy.

A female of childbearing potential is any woman, regardless of sexual orientation or whether they have undergone tubal ligation, who meets the following criteria: 1) has not undergone a hysterectomy or bilateral oophorectomy; or 2) has not been naturally postmenopausal for at

least 24 consecutive months (i.e., has had menses at any time in the preceding 24 consecutive months).

Female? _____ (Yes or No)

Date of blood test or urine study: _____

_____ 3.2.8 The effects of nivolumab on the developing human fetus are unknown. For this reason women of childbearing potential and sexually active males must be strongly advised to use accepted and effective methods of contraception, as described in the Informed Consent Form (ICF) and in Appendix VIII, or to abstain from sexual intercourse for the duration of their participation in the study. Local laws and regulations may require use of alternative and /or additional contraceptive methods. Women of childbearing potential should use adequate methods to avoid pregnancy for 23 weeks after the last dose of nivolumab. Sexually active males should use adequate methods to avoid pregnancy for 31 weeks after the last dose of nivolumab.

_____ 3.2.9 Patient must have no prior history of RCC that was resected with curative intent within the past 5 years.

_____ 3.2.10 Patients must not have other current malignancies:

- Adequately treated basal cell or squamous cell skin cancer, in situ cervical cancer, adequately treated Stage I or II cancer from which the patient is currently in complete remission, or any other cancer from which the patient has been disease-free for 3 years prior to the time of registration and they are not receiving any current treatment.
- Prior or current prostate cancer is excluded.
    - A history of superficial Ta urothelial cancer is permitted (not being currently treated) but T1 or greater disease is excluded.

_____ 3.2.11 No active known or suspected autoimmune disease. The following are permitted: patients with vitiligo, type I diabetes mellitus, residual hypothyroidism due to autoimmune or non-autoimmune condition requiring hormone replacement, asymptomatic hypothyroidism not requiring treatment, psoriasis not requiring systemic treatment, or conditions not expected to recur.

_____ 3.2.12 No ongoing condition requiring systemic treatment with either corticosteroids (> 10 mg daily prednisone equivalent) or other immunosuppressive medications with the exceptions outlined below. No treatment with other immunosuppressive agents within 14 days prior to the first dose of study drug. Topical, ocular, intra-articular, intranasal, inhaled steroids and adrenal replacement steroid doses > 10 mg daily prednisone or the equivalent are permitted in the absence of active autoimmune disease. A brief (less than 3 weeks) course of corticosteroids (any amount) for prophylaxis (for example: contrast dye allergy) or for treatment of non-autoimmune conditions (for example: delayed-type hypersensitivity reaction caused by a contact allergen) is permitted if > 14 days since last dose.

_____ 3.2.13 No uncontrolled adrenal insufficiency

_____ 3.2.14 No known chronic active liver disease or evidence of acute or chronic Hepatitis B Virus (HBV) or Hepatitis C (HCV)

_____ 3.2.15 Patients must not have a serious intercurrent illness, including ongoing or active infection requiring parental antibiotics.

_____ 3.2.16 No known evidence of HIV infection, since the effects of nivolumab on anti-retroviral therapy have not been studied.

_____ 3.2.17 No known medical condition (e.g. a condition associated with uncontrolled diarrhea such as ulcerative colitis or acute diverticulitis) that, in the investigator's opinion, would increase the risk associated with study participation or interfere with the interpretation of safety results

_____ 3.2.18 No major surgery within 28 days prior to randomization

_____ 3.2.19 Patients currently enrolled in other clinical trials testing a therapeutic intervention.

_____ 3.2.20 Patients must have the following baseline laboratory values within 4 weeks of randomization:

_____ 3.2.20.1 White blood cells ≥ 2000/uL

WBC:_____ Date of test:_____

_____ 3.2.20.2 Absolute Granulocyte Count (AGC) ≥ 1,500/mm^3

AGC:_____ Date of test:_____

_____ 3.2.20.3 Platelet Count ≥ 100,000/mm^3

Platelet count:_____ Date of test:_____

_____ 3.2.20.4 Hemoglobin ≥ 9.0g/dL

Hemoglobin:_____ Date of test:_____

_____ 3.2.20.5 Serum creatinine ≤ 1.5 x upper limit of normal (ULN) or calculated creatinine clearance (CrCl) ≥ 40mL/min (CrCl= Wt (kg) x (140-age)*/72 x Cr. level, *female x 0.85)

Serum creatinine: _____ Date of test:_____
ULN:_____

CrCL:_____ Date of test:_____

_____ 3.2.20.6 Total Bilirubin ≤ 1.5 x ULN (except subjects with Gilbert Syndrome, who can have total bilirubin < 3.0 x ULN)

Total bilirubin:_____ Date of test:_____ ULN:_____

_____ 3.2.20.7 AST and ALT ≤ 2.5 x ULN

AST:_____ Date of test:_____ ULN:_____

AST:_____ Date of test:_____ ULN:_____

_____ 3.2.21 No history of severe hypersensitivity to a monoclonal antibody

_____ 3.2.22 Signed, dated informed consent

_____ _____

Physician Signature Date

OPTIONAL: This signature line is provided for use by institutions wishing to use the eligibility checklist as source documentation.