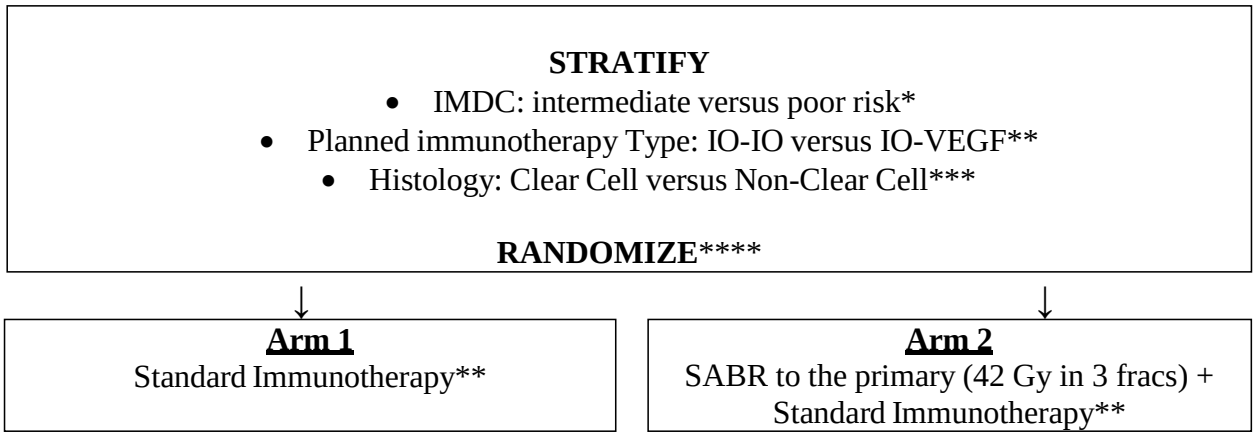
NRG-GU012
SCHEMA



* International Metastatic RCC database consortium (IMDC): Intermediate risk is 1-2 risk factors and poor risk is 3 or more risk factors (See Section 3.1.3).

****** Standard immunotherapy includes the following combinations: IO-IO (Immuno-Oncology): defined as receipt of nivolumab + ipilimumab; Immuno-Oncology-vascular endothelial growth factor) (IO-VEGF): defined as receipt of pembrolizumab + axitinib, avelumab + axitinib, nivolumab + cabozantinib, or pembrolizumab + lenvatinib

*** Maximum accrual of non-clear cell is 48 patients.

****Randomization is 2:1 favoring the experimental arm (Arm 2).

3. ELIGIBILITY AND INELIGIBILITY CRITERIA

Notes: Per NCI guidelines, exceptions to inclusion and exclusion criteria are not permitted. For questions concerning eligibility see protocol cover page. For radiation therapy-related eligibility questions, please contact RTQA (see protocol cover page).

3.1 Eligibility Criteria

A patient cannot be considered eligible for this study unless ALL of the following conditions are met.

3.1.1 Pathologically (histologically or cytologically) proven diagnosis of renal cell carcinoma prior to registration;

3.1.2 Node-positive unresectable (TxN1Mx) or metastatic (TxNxM1) based on the following diagnostic workup:

- History/physical examination within 45 days prior to registration;
- CT/MRI of the chest/abdomen/pelvis within 45 days prior to registration;

3.1.3 Patients must have IMDC intermediate (1-2 factors) or poor risk disease ($\geq$3 factors) (See Appendix I).

3.1.4 Patients with a prior or concurrent malignancy whose natural history or treatment does not have the potential to interfere with the safety or efficacy assessment of the investigational regimen are eligible for this trial.

3.1.5 Patients with measurable disease (node positive or metastatic) as defined by RECIST version 1.1 excluding the primary renal tumor.

3.1.6 Patient not recommended for or refused immediate cytoreductive nephrectomy.

3.1.7 Candidate for standard of care therapy with either IO-IO or IO-VEGF combination regimen.

3.1.8 Primary renal tumor measuring 8 cm or less in anterior to posterior dimension only on axial imaging.

3.1.9 Age $\geq$ 18;

3.1.10 Karnofsky Performance Status $\geq$ 60 within 45 days prior to registration;

3.1.11 Adequate hematologic function within 45 days prior to registration defined as follows:

- Hemoglobin $\geq$ 8 g/dL (transfusions are allowed)
- Platelet count $\geq$ 50,000/mm^3
- ANC $\geq$ 1500/mm^3

3.1.12 Adequate renal function within 45 days prior to registration defined as follows:

- Calculated (Calc.) creatinine clearance $\geq$ 30 mL/min.

Creatinine Clearance (CrCl) ≥30 mL/min estimated by Cockcroft-Gault Equation:

$$\text{CrCl (mL/min)} = \frac{[140 - \text{age (years)}] \times \text{weight (kg)}}{72 \times \text{serum creatinine (mg / dL)}} \quad \{\times 0.85 \text{ for female patients}\}$$

For African American patients specifically whose renal function is not considered adequate by the formula above, an alternative formula that takes race into account (Chronic Kidney Disease Epidemiology Collaboration CKD-EPI formula) should be used for calculating the related estimated glomerular filtration rate (GFR) with a correction factor for African American race creatinine clearance for trial eligibility, where GFR≥30 mL/min/1.73m^2 will be considered adequate:

$GFR = 141 \times \min(S_{cr}/\kappa, 1)^{-0.411} \times \max(S_{cr}/\kappa, 1)^{-1.209} \times 0.993^{Age} \times 1.159$ [if patient identifies as African American]
where:
S_{cr} is serum creatinine in mg/dL,
κ is 0.9 for males,
min indicates the minimum of S_{cr}/κ or 1, and
max indicates the maximum of S_{cr}/κ or 1

A calculator for this formula is available at: https://www.niddk.nih.gov/health-information/professionals/clinical-tools-patient-management/kidney-disease/laboratory-evaluation/glomerular-filtration-rate-calculators/ckd-epi-adults-conventional-units

3.1.13 Adequate hepatic function within 45 days prior to registration defined as follows:

- Total bilirubin $\leq$ 1.5 x upper limit of normal (ULN). (except subjects with Gilbert Syndrome, who can have total bilirubin < 3.0 mg/dL)
- Aspartate aminotransferase and alanine aminotransferase (AST and ALT) $\leq$ 3 x upper limit of normal (ULN) or < 5 x ULN if hepatic metastases present.

3.1.14 Patients with known human immunodeficiency virus (HIV) on effective anti-retroviral therapy with undetectable viral load within 6 months are eligible for this trial. Testing is not required for entry into protocol.

3.1.15 For patients with evidence of chronic hepatitis B virus (HBV) infection, the HBV viral load must be undetectable on suppressive therapy, if indicated.

3.1.16 Patients with a history of hepatitis C virus (HCV) infection must have been treated and cured. Patients with HCV infection who are currently on treatment are eligible if they have an undetectable HCV viral load.

3.1.17 The patient must agree to use a highly effective contraception, including men with vasectomies if they are having sex with a woman of childbearing potential or with a woman who is pregnant, while on study drug and for 6 months following the last dose of study drug. Childbearing potential is defined as any person who has experienced menarche and who has not undergone surgical sterilization (hysterectomy or bilateral oophorectomy) or who is not postmenopausal. Please see section 9 for more details.

3.1.18 The patient or a legally authorized representative must provide study-specific informed consent prior to study entry and, for patients treated in the U.S., authorization permitting release of personal health information.

3.2 Ineligibility Criteria

Patients with any of the following conditions are NOT eligible for this study.

3.2.1 Patients with planned treatment of all metastatic disease with definitive therapy including either surgery, ablative (non-palliative) doses of radiation, or intervention of some type (definitive interventional radiology techniques) to ALL metastatic sites rendering the patient without extra-renal measurable disease. Patients **NOT** planned for definitive treatment of all metastatic sites are eligible. Lesions radiated palliatively are not eligible for response assessment (see section 13).

3.2.2 Patients with untreated or unstable brain metastases or cranial epidural disease.
Note: Patients who have been adequately treated with radiotherapy, radiosurgery, or surgery and stable for at least 4 weeks prior to registration as documented by MRI or CT imaging or deemed stable by clinical investigator are eligible. Treated brain metastases are defined as having no ongoing requirement for steroids and no evidence of progression or hemorrhage after treatment for at least 4 weeks prior to registration as documented by MRI or CT imaging or deemed stable by clinical investigator.

3.2.3 Prior radiotherapy to the kidney that would result in overlap of radiation therapy fields treatment of the primary tumor;

3.2.4 Any prior systemic therapy for metastatic renal cell carcinoma (RCC) note that prior chemotherapy for a different cancer is allowed (completed > 3 years prior to registration);

3.2.5 Severe, active comorbidity defined as follows:

- Active autoimmune disease requiring ongoing therapy including systemic treatment with corticosteroids (> 10 mg daily prednisone equivalents) or other immunosuppressive medications daily. Inhaled steroids and adrenal replacement steroid doses > 10 mg daily prednisone equivalents are permitted in the absence of active autoimmune disease.
- History of severe allergic, anaphylactic or other hypersensitivity reactions to chimeric or humanized antibodies
- Active tuberculosis (PPD response without active TB is allowed)
- Uncontrolled hypertension (systolic BP ≥190mmHg or diastolic BP >110mmHg)
- Major surgery ≤ 45 days prior to registration.
- Any serious (requiring hospital stay or long term rehab) non-healing wound, ulcer, or bone fracture within 45 days prior to registration
- Any arterial thrombotic (STEMI, NSTEMI, CVA, etc) events within 180 days prior to registration
- Active NY Heart Association Class 3-4 heart failure symptoms
- Moderate or severe hepatic impairment (child-Pugh B or C)
- Any history of untreated pulmonary embolism or deep venous thrombosis (DVT) within 180 days prior to registration. (Any asymptomatic or treated pulmonary embolism or asymptomatic treated deep venous thrombosis >30 days prior to registration is allowed). See section 5.3 for more details.
- Unstable cardiac arrhythmia within 180 days prior to registration
- History of abdominal fistula, gastrointestinal perforation, intra-abdominal abscess, bowel obstruction, or gastric outlet obstruction within 180 days prior to registration
- History of or active inflammatory bowel disease.
- Malabsorption syndrome within 45 days prior to registration

3.2.6 Pregnancy and individuals unwilling to discontinue nursing. For women of child bearing potential must have a negative pregnancy test ≤ 45 days prior to registration.