FAST FACTS

S1931 - PHASE III TRIAL OF IMMUNOTHERAPY-BASED COMBINATION THERAPY WITH OR WITHOUT CYTOREDUCTIVE NEPHRECTOMY FOR METASTATIC RENAL CELL CARCINOMA (PROBE TRIAL)

ELIGIBILITY CRITERIA
STEP 1 REGISTRATION

a. Disease Related Criteria

1. Participants must have a histologically proven diagnosis of clear cell or non-clear cell renal cell carcinoma. Participants with collecting duct carcinoma histology are not eligible. Participants with multifocal or bilateral tumors are eligible.
2. Participants must have primary tumor in place.
3. Participants must have the following scans performed, showing clinical evidence of measurable or non-measurable metastatic disease:
   - **CT scan of the chest (can be performed without contrast if CT contrast cannot be given)**
   - CT of abdomen and pelvis with contrast OR MRI of the abdomen and pelvis with or without contrast

   Scans must be performed within the following timeframes:
   - Immunotherapy naïve participants must have scans documenting metastatic disease completed within 90 days prior to study registration.
   - Pre-randomization completed participants must have scans documenting metastatic disease completed within 90 days prior to first dose of systemic immunotherapy treatment.
4. Participants with treated brain metastases are must have no evidence of progression on follow-up brain imaging after CNS-directed therapy. Brain imaging studies are not required unless clinically indicated.

b. Prior/Concurrent Therapy Criteria

1. Participants must not have received the following prior treatment of metastatic renal cell carcinoma:
   - Immunotherapy naïve participants must not have received any prior lines of systemic immunotherapy for metastatic renal cell carcinoma.
   - Pre-randomization completed participants must not have received any systemic immunotherapy therapy for metastatic renal cell carcinoma beyond the one regimen received off protocol as specified in Step 1 pre-randomization treatment (see Section 7.1).
2. Participants must not have received more than the following amounts protocol-directed pre-randomization treatment:
   - Immunotherapy naïve participants must not have received any pre-randomization treatment.
   - Pre-randomization completed participants must not be planning to receive any additional treatment prior to Step 2 randomization, and must not have received more than the following amounts of pre randomization treatment

- 5 total: infusions of nivolumab at 3 mg/kg plus 1 dose (240 mg of 480 mg)
- 7 infusions of nivolumab at 248mg dose
- 4 infusions of nivolumab at 480mg dose
- 4 infusions of ipilimumab
- 5 infusions of pembrolizumab at 200mg dose
- 3 infusions of pembrolizumab at 400mg dose
- 7 infusions of avelumab

3. Participants must not have received immunotherapy for any cancer within the following timeframes:
   - Immunotherapy naïve participants must not have received any immunotherapy within 6 months prior to registration.
   - Pre-randomization completed participants must not have received any other immunotherapy within 6 months of the start of protocol specified pre- randomization treatment (see Section 7.1).
4. Participants with symptomatic metastases may have received palliative radiotherapy or receive palliative radiotherapy after registration.
5. Participants must have no clear contraindications to nephrectomy.

c. Clinical Laboratory Criteria

1. Participants must be ≥ 18 years old.
2. Participants must not have a solitary kidney and not have a transplanted kidney.
3. No other prior malignancy is allowed except for the following: adequately treated basal cell or squamous cell skin cancer, any in situ or T1 cancer, adequately treated Stage I or II cancer from which the participant is currently in complete remission, or any other cancer from which the participant has been disease free for at least two years.
4. Participants must not have been previously diagnosed with a medical condition that makes them ineligible for immune based combination therapy or nephrectomy.

2. STEP 2 RANDOMIZATION

a. Disease Related Criteria

1. Participants must have at least one of the following scans performed 12 weeks (+/- 2 weeks) after starting pre-randomization immunotherapy treatment.
   - CT scan of the chest (can be performed without contrast if CT contrast cannot be given)
   - CT of abdomen and pelvis with contrast OR MRI of the abdomen and pelvis with or without contrast

   Scans must be performed within 28 days prior to randomization. Response should be assessed by comparing with a CT or MRI of the chest, abdomen and pelvis obtained prior to starting pre-randomization immunotherapy treatment. Participants with complete response in all metastatic sites are not eligible to randomize to Step 2.
2. Participants must have one of the following objective statuses after 12 weeks of pre-randomization immunotherapy treatment.
   - stable disease

- partial response
- the treating investigator believes the participant is deriving clinical benefit from systemic immunotherapy AND have Zubrod performance status 0-1.

3. Participants must plan to continue the immune-based therapy received during pre-randomization immunotherapy treatment.
4. Participants must not show progression in the primary tumor (see Section 10.6). Participants who are considered to have pseudo progression (see Section 10.2b) are allowed.
5. Participants with treated brain metastases must have no evidence of progression on follow-up brain imaging after CNS-directed therapy. Brain imaging studies are not required, unless clinically indicated.

b. Prior/Concurrent Therapy Criteria

1. Participants must be registered to Step 2 Randomized on or between week 11, Day 1, and week 14, Day 7 of protocol-directed pre-randomization immunotherapy treatment.
2. Participants must have received at least one of the minimum amounts of immunotherapy:
   - 2 infusions of nivolumab + 1 infusion of ipilimumab (if given in combination)
   - 2 infusions of pembrolizumab at 200mg dose
   - 1 infusion of pembrolizumab at 400mg dose
   - 2 infusions of avelumab
   - 2 infusions of nivolumab (if not given in combination with ipilimumab)
3. Participants must have a planned surgery date within 42 days of randomization.

c. Clinical Laboratory Criteria

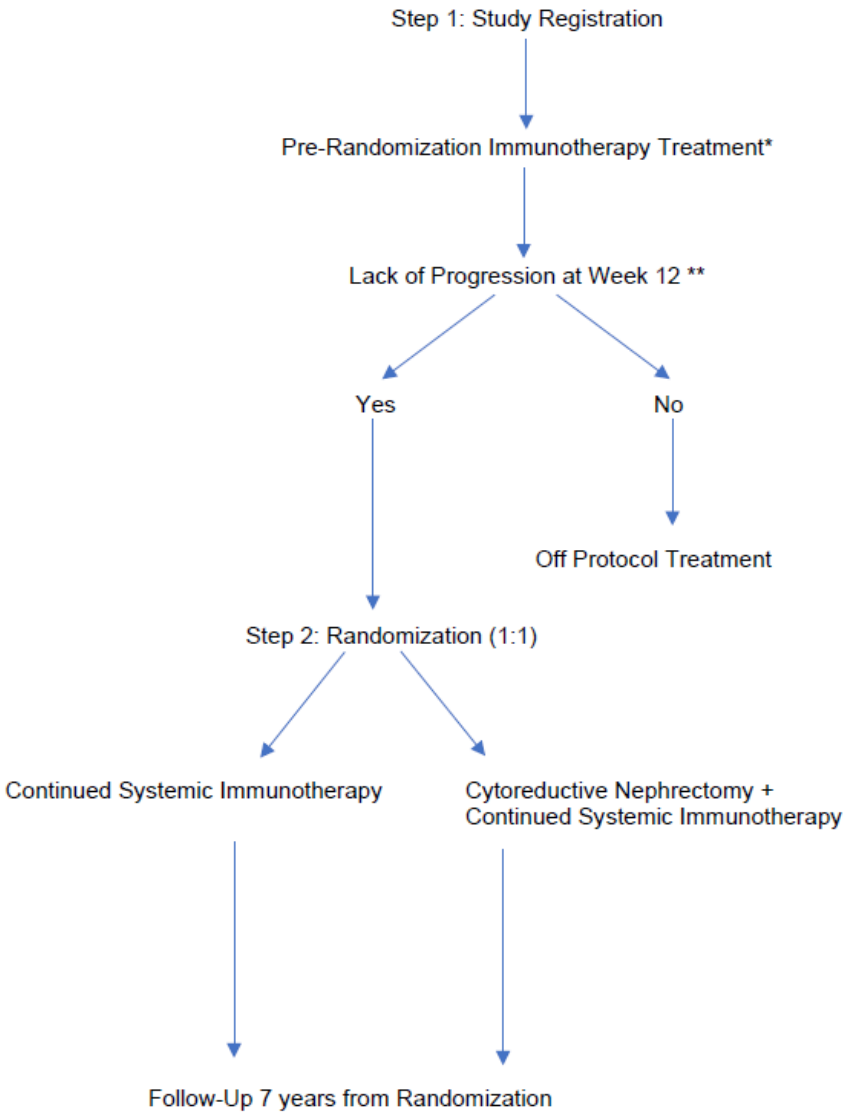
1. Participants must be a surgical candidate as determined by study urologist. The urology consult must be done within 42 days prior to randomization.
2. Participants must have a complete physical examination and medical history within 28 days prior to randomization.
3. Participants must have a Zubrod performance status of 0-1 within 28 days prior to randomization (see Section 10.6).
4. Participants must have adequate liver function within 28 days prior to randomization as defined below:
   - total bilirubin ≤ 2 x institutional upper limit of normal (ULN)
   - AST≤3 × institutional ULN, unless liver metastases. Participants with liver metastases must have ALT ≤5 × institutional ULN
   - ALT ≤3 × institutional ULN, unless liver metastases. Participants with liver metastases must have ALT ≤5 × institutional ULN
5. Participants must have a serum creatinine ≤ 1.5x the IULN OR measured OR calculated creatinine clearance ≥ 50 mL/min using the following Cockroft-Gault Formula. This specimen must have been drawn and processed within 28 days prior to randomization:

$$\text{Calculated Creatinine Clearance} = \frac{(140 - \text{age}) \times (\text{weight in kg})\ \dagger}{72 \times \text{serum creatinine}\ *}$$

Multiply this number by 0.85 if the participant is a female.
† The kilogram weight is the participant weight with an upper limit of 140% of the IBW.
* Actual lab serum creatinine value with a minimum of 0.8 mg/dL.

6. No other prior malignancy is allowed except for the following: adequately treated basal cell or squamous cell skin cancer, in situ cervical cancer, adequately treated Stage I or II cancer from which the participant is currently in complete remission, or any other cancer from which the participant has been disease free for two years.

SCHEMA


Step 1: Study Registration
Pre-Randomization Immunotherapy Treatment*
Lack of Progression at Week 12 **
Yes
No
Off Protocol Treatment
Step 2: Randomization (1:1)
Continued Systemic Immunotherapy
Cytoreductive Nephrectomy +
Continued Systemic Immunotherapy
Follow-Up 7 years from Randomization