**BACKGROUND and ELIGIBILITY**

**Synchronous Primary Tumor and Metastases**
- Contemporary randomized cytoreductive nephrectomy trials reveal that resection of primary tumor did not improve survival outcomes (CARMENA and SURTIME).
- Sequential trial shows that initial systemic therapy followed by nephrectomy has better survival outcomes than upfront nephrectomy.
- In setting of I-O based regimens the role of nephrectomy has not been evaluated.
- SWOG 1931 (PROBE) trial is addressing this question.

**Immunotherapy-based combinations are proven in the frontline setting and have CR rates as high as 16%**.
- Keeping the primary tumor in place may increase antigen load and make powerful checkpoint inhibition even more effective when activating the immune system.
- The role of cytoreductive nephrectomy is unclear when using immunotherapy.

**ELIGIBILITY**

- **STEP 1. REGISTRATION**
  - Histologically proven renal cell carcinoma (collecting duct carcinoma NOT eligible).
  - Primary tumor in place.
  - Imaging showing measurable or non-measurable metastatic disease within 90d prior to registration.
  - Within 90d prior to first dose of immunotherapy for previously treated patients.
  - No active brain metastases.

- **STEP 2. RANDOMIZATION**
  - Imaging performed 12 (+/- 2) weeks after starting pre-randomization treatment.
  - Patient is deriving clinical benefit from systemic therapy.
  - Surgical candidate per study urologist with surgery scheduled within 42 days of registration.

- **STEP 3. randomization treatment**
  - Within 90d prior to first dose of immunotherapy for previously treated patients.

- **STEP 4. CONSENT**
  - Randomization drug toxicities.
  - No active brain metastases.

- **STEP 5. RANDOMIZATION**
  - Imaging performed 12 (+/- 2) weeks after starting pre-randomization treatment.
  - Patient is deriving clinical benefit from systemic therapy.
  - Surgical candidate per study urologist with surgery scheduled within 42 days of randomization.

- **Within 28 days prior to randomization**
  - No known active brain metastases.
  - Performance status of 0-1.
  - Adequate liver function.

**STUDY DESIGN**

**SWOG 1931/PROBE Trial**

**Primary Endpoint: Overall Survival**

**Statistical Design**

- **Stratification: pre-randomization immunotherapy status at entry, Zubrod PS, systemic agent combination, 12-week disease response.**
- **Only randomized patients (1:1) are assessed for OS**
- **Using Median OS times of 25 months for Control and median OS of 37 months (SurTime showed 17.4 mo OS difference) -- hazard ratio 0.68**
- **Using 85% power, 1-sided alpha =0.025 provides a sample size of 302 eligible patients (364 total assuming 20% not randomized and 10% ineligible)**

**STUDY OBJECTIVES**

**Primary Objective**

To compare overall survival in participants with newly diagnosed metastatic renal cell carcinoma who are randomized to receive immune checkpoint inhibitor-based combination treatment plus cytoreductive nephrectomy versus immune checkpoint inhibitor-based combination treatment alone.

**Secondary Objectives**

- To compare overall survival between arms in the subset who received their assigned protocol treatment.
- To compare investigator assessed progression-free survival between arms.
- To assess complications of nephrectomy and post-randomization drug toxicities.
- To compare objective response rate in metastatic sites between the arms in participants with measurable metastatic disease.
- To assess change in diameter of primary tumor at Week 12 +/- 2 weeks disease assessment in participants who have received pre-randomization treatment.