SWOG S1931 (PROBE): Phase III randomized trial of Immune checkpoint inhibitor (ICI) combination regimen with or without Cytoreductive Nephrectomy (CN) in Advanced Renal Cancer [NCT04510597]

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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 :

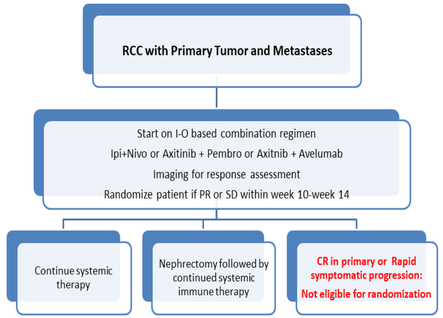
•STEP 1. REGISTRATION
•Histologically proven renal cell carcinoma (collecting duct carcinoma NOT eligible)
•Primary tumor in place.
•Imaging showing measurable or non-measurable metastatic disease within 90d prior to registration
•Within 90d prior to first dose of immunotherapy for previously treated 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 randomization
•Within 28 days prior to randomization:
- No known active brain metastases.
- Performance status of 0-1
- Adequate liver function

STEP 1 and 2 Can Occur Together at 10-14 weeks of starting systemic therapy

STUDY DESIGN

SWOG 1931/PROBE Trial
Primary Endpoint: Overall Survival



Statistical Design

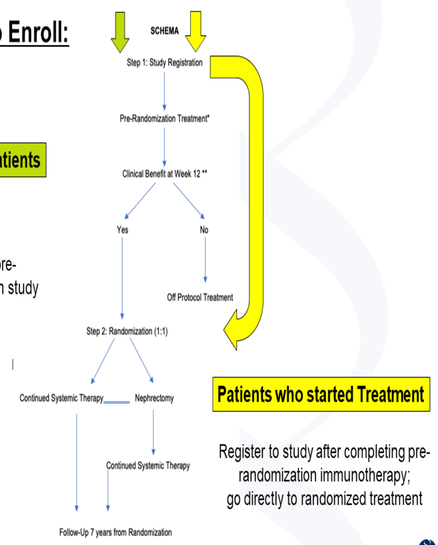
- Stratification: pre-randomization immunotherapy status at entry, Zubrod PS, systemic agent combination, 12-week disease response.
- Only randomized patients (1:1) are assessed for OS
- Using Median OS times of 25 months for Control and median OS of 37 months (SurTime showed 17.4 mo OS difference) -- 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 DESIGN

Two Opportunities to Enroll:

Treatment Naïve Patients

Register to study & receive pre-randomization immunotherapy on study



Patients who started Treatment

Register to study after completing pre-randomization immunotherapy; go directly to randomized treatment

Leading cancer research. **Together.**

SWOG

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Statisticians: *Cathy Tangen, DrPH and Eddie Mayerson, MS*
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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.