Accrual goal = 805 patients.
Cycle length = 28 days.
If trial participation began prior to Addendum 4, then patients may receive more doses given the 2-week treatment intervals, but no more than 2 doses of neoadjuvant therapy (no more than 480 mg total) and 9 months of adjuvant therapy.

*Only oligometastatic disease permitted and defined as ≤ 3 metastases that can be resected or treated at the same time as nephrectomy or within a 12-week window.
†Patients randomized to arm H must either have RCC confirmed by a standard-of-care biopsy prior to registration, or, if a biopsy was not already performed, have a research biopsy after randomization to arm H. RCC confirmation is required to avoid exposing patients to neoadjuvant nivolumab who clearly have a benign lesion or another type of cancer.
‡Patients randomized to arm O are encouraged, but not required, to have a biopsy prior to or after randomization.
§Neoadjuvant (preoperative) nivolumab dosing: 480 mg IV must be administered within 4 weeks of registration and prior to partial or radical nephrectomy. Adjuvant (postoperative) nivolumab dosing: total of 9 doses; 1 dose q 4 weeks for 9 months. Perioperative nivolumab dosing: nephrectomy at a minimum of 7 days from neoadjuvant dose, and no more than 28 days. First adjuvant dose within 4 to 10 weeks post-nephrectomy or last local treatment.
||Nephrectomy should be within 8 weeks after registration in the observation arm (arm B).
¶Nephrectomy can be done at any qualified hospital; it does not need to be done at an ECOG-ACRIN or NCTN affiliated center.

EA8143

A Phase 3 RandOmized Study Comparing PERioperative Nivolumab vs. Observation in Patients with Renal Cell Carcinoma Undergoing Nephrectomy (PROSPER RCC)
Overall EA8143 Study Objective
To examine whether the addition of perioperative nivolumab to radical or partial nephrectomy can improve clinical outcomes in patients with renal cell carcinoma (RCC)

Study Objectives

Primary Objective
• Compare recurrence-free survival (RFS) between patients with RCC randomly assigned to perioperative nivolumab in conjunction with radical or partial nephrectomy with patients randomized to surgery alone

Secondary Objectives
• Evaluate RFS in a subset of patients with clear cell histology
• Compare overall survival (OS)
• Evaluate safety and tolerability

Correlative Objectives
• Correlate the primary tumor’s expression of programmed death–ligand 1 (PD-L1) with outcome
• Correlate the expression of PD-L1 on tumor tissue at nephrectomy and recurrence with outcome
• Archive images for potential central confirmation of recurrence and for future correlative work with ACRIN, including markers predicting outcome or response
• Prospectively collect tumor and biologic specimens (eg, serum, peripheral blood mononuclear cells [PBMCs])

Quality of Life Objective
• Evaluate differences in change from baseline in patient-reported symptoms and toxicities among patients randomized to treatment with nivolumab compared with surgery alone

Exploratory Objectives
• Characterize pharmacokinetics of nivolumab and explore exposure response relationships with respect to safety and efficacy
• Characterize immunogenicity of nivolumab
• Explore descriptively the efficacy of nivolumab treatment in patients with non-clear cell (including unclassified) histologies
• Characterize the effects of nivolumab on bone metabolism and bone density
Eligibility Criteria*

Main Inclusion Criteria

Preregistration and Randomization (Step 0)
- A renal mass consistent with a clinical stage ≥ T2Nx RCC or TanyN+ RCC for which radical or partial nephrectomy is planned
- If histologic confirmation of RCC was not done within 12 months prior to preregistration, must undergo a core biopsy if randomized to arm H. This can be a standard-of-care diagnostic biopsy or a research biopsy following arm H assignment or planned metastasectomy before or after randomization. If biopsy after preregistration (step 0) is benign, oncocytoma, or a different cancer, then ineligible for step 1
- If randomized to arm O, then permitted to register to step 1, regardless of having a standard-of-care diagnostic biopsy
- ≥ 18 years of age
- ECOG performance status 0 or 1
- Adequate hematologic, hepatic, and renal function within 8 weeks of registration
- Use of effective contraception

Main Exclusion Criteria
- Clinical or radiologic evidence of distant metastases (M0) unless the presumed M1 disease is planned to be resected or definitively treated at the time of or within a 12-week window from the date of initial procedure such that the patient is considered “no evidence of disease” (M1 NED)
- Prior systemic or local anticancer therapy for the current RCC. Prohibited therapies for RCC include partial nephrectomy for the current RCC; metastasectomy for the current RCC unless performed to render patient NED within 6 months of current diagnosis; radiation therapy to the bilateral kidney or any distant metastatic sites unless administered to render patient NED within 6 months of current diagnosis; current or past antineoplastic systemic therapy for RCC; 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 costimulation or checkpoint pathways
- Prior history of RCC that was resected with curative intent within the past 5 years

*When evaluating patients for this study, please refer to the full protocol for the complete list of eligibility criteria.
Eligibility Criteria*

Main Exclusion Criteria (cont)

- Concurrent malignancies, with exceptions
- Active known or suspected autoimmune disease, with exceptions
- Ongoing condition requiring systemic treatment with either corticosteroids (> 10 mg/d prednisone equivalent) or other immunosuppressive medications, with exceptions
- Uncontrolled adrenal insufficiency
- Chronic active liver disease or evidence of acute or chronic hepatitis B or C virus
- Serious intercurrent illness, including ongoing or active infection requiring parenteral antibiotics
- HIV positivity
- Known medical condition (e.g., condition associated with uncontrolled diarrhea) that, in the investigator’s opinion, would increase the risk associated with study participation or interfere with the interpretation of safety results
- Major surgery within 28 days prior to randomization
- Current enrollment in another clinical trial evaluating a therapeutic intervention
- History of severe hypersensitivity to a monoclonal antibody
- Pregnancy or breastfeeding

*When evaluating patients for this study, please refer to the full protocol for the complete list of eligibility criteria.