

The future of perioperative therapy in advanced renal cell carcinoma: how can we PROSPER?

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Patients with high-risk renal cell carcinoma (RCC) experience high rates of recurrence despite definitive surgical resection. Recent trials of adjuvant tyrosine kinase inhibitor therapy have provided conflicting efficacy results at the cost of significant adverse events. PD-1 blockade via monoclonal antibodies has emerged as an effective disease-modifying treatment for metastatic RCC. There is emerging data across other solid tumors of the potential efficacy of neoadjuvant PD-1 blockade, and preclinical evidence supporting a neoadjuvant over adjuvant approach. PROSPER RCC is a Phase III, randomized trial evaluating whether perioperative nivolumab increases recurrence-free survival in patients with high-risk RCC undergoing nephrectomy. The neoadjuvant component, intended to prime the immune system for enhanced efficacy, distinguishes PROSPER from other purely adjuvant studies and permits highly clinically relevant translational studies.

Lay abstract: While many patients with early stage kidney cancer can be cured by removal of the tumor and kidney ('nephrectomy'), upward of 40% of patients can recur due to microscopic spread of the cancer prior to surgery. Adding anticancer drugs that are effective in the metastatic setting to surgery has potential to eliminate the microscopic disease and increase cure rates. The PROSPER renal cell carcinoma

study is testing whether adding nivolumab, a drug that engages the immune system to better recognize, fight and eliminate the cancer, will improve disease control over surgery alone. Nivolumab will be given before and after surgery to see if it reduces the chance of the disease returning and decreases death from kidney cancer compared with patients receiving surgery only.

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Due to an increase in both risk factors and incidental diagnoses, the worldwide incidence of kidney cancer rose for almost 30 years before its recent stabilization [1]. In the USA, >60,000 patients are diagnosed with kidney cancer yearly with renal cell carcinoma (RCC) representing the most common entity and 30% of patients initially presenting with clinical stage II disease (T2N0M0) or greater [2]. While many with nonmetastatic RCC can be cured with surgery, upward of 40% recur due to micrometastatic disease at the time of surgery [3]. To address this clinical need, multiple trials have investigated the addition of systemic therapy after surgery in nonmetastatic disease based on effectiveness in the metastatic setting [4]. However, despite over 13 randomized trials testing adjuvant systemic therapies in the last 40 years [5], there has been only one positive study. In this trial highlight, we discuss the recent controversy over the adjuvant use of targeted therapies and highlight the ongoing trials of perioperative immune checkpoint blockade with a focus on the PROSPER RCC Study.

Adjuvant targeted therapy

Advances in systemic therapy for RCC with targeted therapies, such as sunitinib and pazopanib, developed against the hypoxia inducible factor pathway integral in RCC development have improved outcomes for patients with metastatic disease [6]. Therefore, moving these agents earlier to the adjuvant setting with the goal of eliminating micrometastatic disease was a natural and rationale choice for patients at high risk of recurrence.

Six trials testing adjuvant tyrosine kinase inhibitors (TKI) or mTOR inhibition were undertaken and four have reported with conflicting results (Table 1) [7–10]. The first was the ASSURE trial (ECOG-ACRIN E2805), a three-arm Phase III study which randomized 1943 patients with pT1b (grade 3–4), pT2–4 or TanyN+ M0 disease to sunitinib, sorafenib or placebo for 54 weeks of treatment. Clear cell and nonclear cell diseases were permitted. There was no difference in disease-free survival (DFS) or overall survival (OS) with a median follow-up of 5.8 years [8]. In addition, 63% of patients assigned to treatment experienced grade 3 or worse adverse events, 45% required dose reduction when starting at the full dose (32% when starting at the reduced dose) and 51% discontinued therapy early compared with 29% assigned to placebo. Soon thereafter, results from S-TRAC, a Phase III study which randomized 615 M0 patients (pT3–4 or TanyN+) to sunitinib or placebo, demonstrated improved DFS (hazard ratio [HR]: 0.76 [0.59–0.98]; $p = 0.03$) but no difference in OS at a median follow-up of 5.4 years [10]. S-TRAC had some notable differences in eligibility and dosing compared with ASSURE, which may account for the disparate results. It included a somewhat higher risk population with clear cell only disease, started all patients on full dose sunitinib, and did not allow dose reductions as low as ASSURE. Further, S-TRAC required blinded independent central radiologic review. Despite these differences, upon *post hoc* retrospective analyses of the ASSURE study in patients with a phenotype similar to S-TRAC (i.e., \geq pT3, clear cell histology or patients receiving higher dose intensity), the ASSURE investigators continued to see no differences in recurrence-free survival (RFS) [11].

The Phase III PROTECT trial investigated 1 year of adjuvant pazopanib (800 mg) versus placebo in 1538 patients with pT2 (grade 3–4), pT3–4 or TanyN1 disease [9]. The primary end point was amended early in the trial to be DFS at a lower starting dose of 600 mg daily due to toxicity issues such as liver dysfunction. No statistically significant difference in DFS was observed at the 600 mg dosing compared with placebo ($n = 1135$; HR: 0.862 [0.699–1.063]; $p = 0.165$). The PROTECT study highlighted that dose intensity may matter as a DFS benefit was observed among the 403 patients receiving 800 mg of pazopanib (HR: 0.693 [0.510–0.943]; $p < 0.05$) and in the overall cohort of 1538 patients (HR: 0.802 [0.675–0.954]; $p < 0.05$). However, no benefit in OS has yet been demonstrated among any subset or the total cohort.

Notably, a fourth Phase III trial evaluating 1 year of adjuvant axitinib (ATLAS) was recently stopped early due to futility for the DFS primary end point. Complementary to S-TRAC, subset analysis of ATLAS suggested a

Table 1. Clinical trials evaluating adjuvant tyrosine kinase and mTOR inhibition for renal cell carcinoma.

Trial	Status	Treatments compared	Stage for inclusion	Histology	Primary outcome	Ref.
ASSURE	Reported	Sunitinib, sorafenib or placebo for 54 weeks	pT1b (grade 3–4), pT2-4 or TanyN1	Clear cell or nonclear cell	DFS; no difference	[8]
S-TRAC	Reported	Sunitinib or placebo for 1 year	pT3-4 or TanyN1	Clear cell only	DFS; improved (HR: 0.76 [0.59–0.98]; p = 0.03) for sunitinib	[10]
PROTECT	Reported	Pazopanib or placebo for 1 year	pT2 (grade 3–4), pT3-4, or TanyN1	Clear cell or predominantly clear cell	DFS; no difference	[9]
ATLAS	Reported	Axitinib or placebo for 1–3 years	pT2 or TanyN1	Clear cell or predominantly clear cell	DFS; no difference, stopped early for futility	[7]
SORCE	Ongoing	Sorafenib (3 years), sorafenib (1 year) or placebo	Leibovich score 3–11	Clear cell or nonclear cell	DFS; ongoing	NCT00492258
EVEREST	Ongoing	Everolimus or placebo for 54 weeks	pT1b (grade 3–4), pT2-4 or TanyN1	Clear cell or nonclear cell	RFS; ongoing	NCT01120249

DFS: Disease-free survival; HR: Hazard ratio; RFS: Recurrence-free survival.

potential benefit in the highest-risk subpopulation [7]. Overall, ASSURE, S-TRAC, PROTECT and ATLAS provide conflicting evidence on whether adjuvant TKI therapy improves DFS for patients with high-risk, nonmetastatic RCC, but all show that any benefit would come at the cost of potentially significant side effects and without assurance of a survival benefit at 5-years. Across these trials, approximately 30–50% discontinued drug due to toxicity [8–10].

A decade after its approval for metastatic RCC, and based on the positive DFS results of S-TRAC, sunitinib was approved in November 2017 by the US FDA for the adjuvant treatment of high-risk clear cell RCC after nephrectomy. Despite the approval of sunitinib, many practitioners remain conflicted due to the potential toxicity and lack of proven OS benefit. Indeed, a panel of experts and patients advocates from the European Association of Urology (EAU) does not recommend its use believing its side effects may outweigh the potential benefit [12]. The NCCN gives it a class 2B rating citing lower level evidence [13].

Adjuvant checkpoint blockade

RCC has been long recognized as an immunotherapy sensitive cancer based on the modest successes and rare but real complete responses to therapies in the cytokine era such as IFN- α and high dose IL-2 [4,14,15]. Modern immunotherapies directed against immune checkpoints have recently transformed the treatment paradigm for RCC. PD-1 is a physiologic immune checkpoint that cancers have used to their advantage when they upregulate PD-L1 on their tumor surface. When engaged by tumor PD-L1, it can lead to T-cell anergy or apoptosis permitting tumor cells to avoid destruction [16].

Nivolumab, an antibody to PD-1, was the first checkpoint inhibitor shown to be effective in metastatic RCC. In the Phase III Checkmate 025 study for patients with antiangiogenic-refractory metastatic RCC, nivolumab significantly improved OS and objective response rates compared with everolimus [17]. It also demonstrated a better adverse event profile compared with everolimus (19 vs 37% grade 3–4 events). The landscape shifted yet again recently with the results from Checkmate 214 which demonstrated a significant objective response rates and OS benefit for the combination of ipilimumab and nivolumab over sunitinib in the first-line setting for intermediate- and poor-risk patients [18]. These results have led the EAU and FDA to declare the combination of monoclonal antibodies against CTLA-4 and PD-1, ipilimumab and nivolumab, as a new standard of care for intermediate- and poor-risk metastatic RCC [18,19]. Updated data in the favorable risk subgroup of Checkmate 214 also suggested no significant difference in outcomes between the combination immunotherapy and sunitinib making it a reasonable option in those patients as well [20].

Capitalizing on the success of PD-1 pathway blockade in the metastatic setting and its general tolerability makes moving these agents earlier to the micrometastatic setting, where disease burden is less and the immune system may be more intact, an attractive approach. The enthusiasm has resulted in at least five ongoing Phase III perioperative studies for patients at high-risk of RCC recurrence including evaluation of checkpoint inhibitor combinations such as ipilimumab and nivolumab (Checkmate 914; NCT03138512) and durvalumab with or without tremelimumab (RAMPART; NCT03288532), as well as monotherapy studies such as nivolumab (PROSPER

RCC, NCT03055013), pembrolizumab (KEYNOTE- 564; NCT03142334) and atezolizumab (IMmotion010; NCT03024996). PROSPER and the latter two trials permit patients with limited metastatic burden who can be rendered NED (no evidence of disease) prior to adjuvant therapy to enroll. All but one, the PROSPER RCC study, are purely adjuvant studies.

Perioperative checkpoint blockade: PROSPER RCC

PROSPER RCC (NCT03055013) is a Phase III, randomized trial designed to evaluate the impact of perioperative nivolumab compared with observation on RFS for patients undergoing radical or partial nephrectomy for high-risk RCC. The unblinded study is being conducted by National Clinical Trials Network of the National Cancer Institute (NCI). The study drug is provided by the Bristol-Myers Squibb under a Cooperative Research and Development Agreement with the NCI.

Background & rationale

Although the pure adjuvant approach has been the general strategy for Phase III studies in RCC, a compelling argument can be made for incorporating neoadjuvant therapy, which has been utilized for other urological malignancies including urothelial carcinoma of the bladder and the upper urinary tracts [21–24]. Early data suggest the addition of neoadjuvant pembrolizumab to standard chemotherapy for high-risk breast cancer may triple the rate of pathologic complete response [25]. Similarly, in early stage non-small-cell lung cancer, two doses of preoperative nivolumab induced a significant pathologic complete response rate of 45% [26]. In muscle invasive bladder cancer, preliminary results from the PURE-01 study showed a complete response rate of 40.5% after three cycles of pembrolizumab, and ABACUS reported a 29% complete response rate after two cycles of atezolizumab among patients with urothelial carcinoma undergoing cystectomy [27,28].

Based on the mechanism of PD-1 blockade, RCC is another prime candidate for neoadjuvant PD-1 inhibition which may enhance the antitumor T cell response that is naturally induced by the primary tumor. PD-1 blockade prior to nephrectomy when the tumor ('antigen') is in place has greater potential to augment the immune response compared with blockade after nephrectomy alone (Figure 1). Indeed, in murine models employing an aggressive breast cancer cell line a short course of neoadjuvant immunotherapy improved survival to greater degree than adjuvant therapy, and the primary tumor was required for the expansion of the tumor specific T cells [29]. Elevated tumor-specific CD8⁺ T cells after neoadjuvant treatment were predictive of survival [29].

The PROSPER RCC trial was designed to test a three-pronged approach to treating high-risk RCC by implementing neoadjuvant, surgical and adjuvant therapies [30]. A single-agent strategy was selected to minimize toxicity as patients may be cured by surgery alone. In addition, one neoadjuvant dose of 480 mg of nivolumab (formerly two doses of 240 mg 2 weeks apart) may be inadequate to eliminate all micrometastatic disease that remains after surgery. Thus, PROSPER continues to engage the immune system with 9 months of adjuvant nivolumab. If positive, PROSPER is poised to transform the current treatment paradigm for patients with high-risk RCC.

Design

Study design

PROSPER RCC is a Phase III, randomized trial for patients with high-risk or oligometastatic RCC of any histology comparing the perioperative administration of nivolumab before and after nephrectomy to observation only after nephrectomy (Figure 2). Importantly, the study is unblinded without a placebo control. Patients meeting criteria for randomization will be assigned in a 1:1 fashion to each arm stratified by clinical T, N and M stages. The decision to pursue radical versus partial nephrectomy will be at the surgeon's discretion accounting for patient preference, safety and feasibility.

Given the emphasis on neoadjuvant nivolumab for patients assigned to the treatment arm, inclusion criteria are based on clinical staging rather than the pathologic staging generally employed in adjuvant trials. All patients enrolled in PROSPER RCC and randomized to the neoadjuvant arm will undergo a renal mass biopsy to ensure the patient has RCC. Given the limited ability for standard imaging modalities and composite models to distinguish malignant and benign renal masses, biopsy provides a diagnostic tool with high positive predictive value for malignancy [31,32]. Although all RCC histologies are allowed, nonclear cell histology will be limited to 15% of accrual to retain sufficient power for outcomes in the clear cell RCC subset. Biopsy is encouraged, but not mandated, for patients assigned to the nephrectomy followed by observation arm.

Although RFS is the primary end point, OS will be a key secondary outcome given the negative findings from adjuvant TKI trials to date [8–10]. Surgical pathology is also of interest as 20% of clinical T2N0M0 kidney cancer is known to be upstaged to pT3a following surgery [33]. Pathologic stage distribution, T-cell infiltration and PD-L1 expression via immunohistochemistry in PROSPER RCC should provide insight into the potential impact of neoadjuvant nivolumab on the local tumor and allow exploratory identification of subsets of patients that may derive the greatest benefit.

Eligibility criteria

Key inclusion criteria include age ≥ 18 years, clinical stage $\geq T2N_x$ or TanyN+ disease, good performance status, adequate end organ function and planned to undergo radical or partial nephrectomy. Patients with oligometastatic disease defined as ≤ 3 metastases are permitted if they are planned to undergo local treatment of the metastases within 12 weeks of nephrectomy. Patients with any liver, bone or brain metastases are excluded regardless of number of sites. Local treatments to manage oligometastatic sites include metastasectomy, thermal ablation or stereotactic radiation.

Preoperative biopsy among patients randomized to neoadjuvant nivolumab must demonstrate RCC of any histology. Sarcomatoid features or unclassified histology are permitted. A nondiagnostic biopsy is considered a good

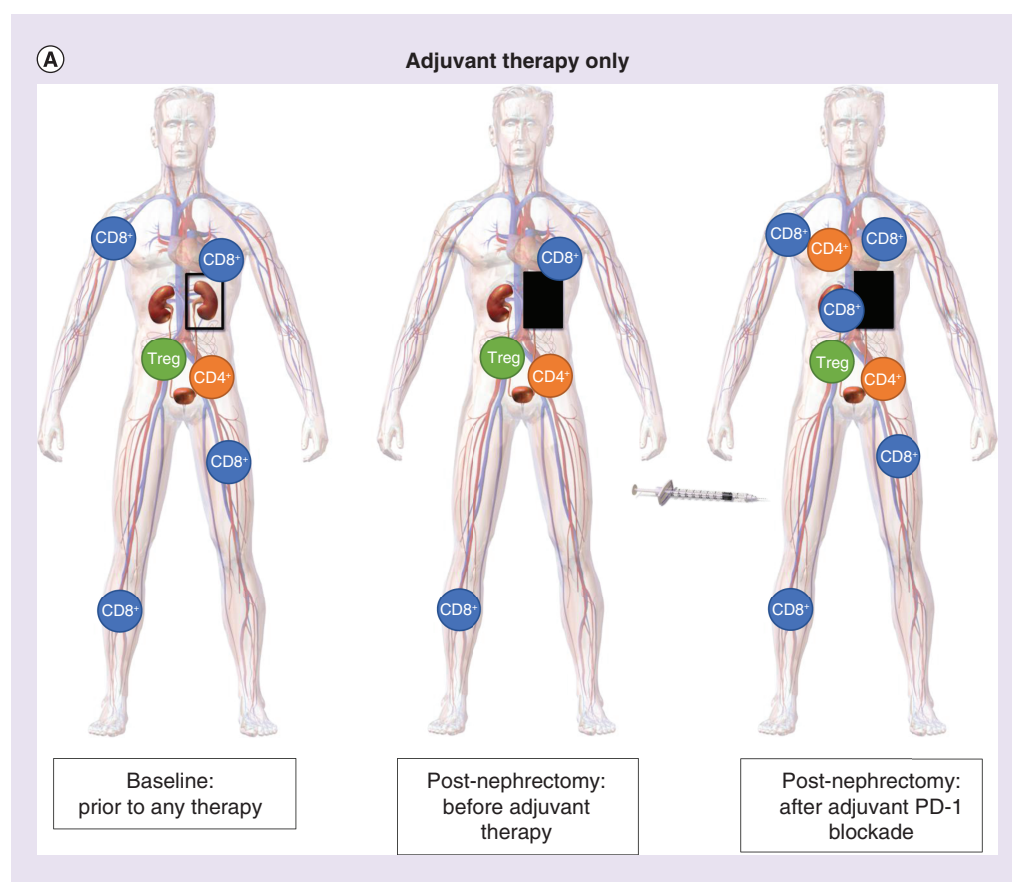


Figure 1. Schematic theoretic representation of the potential immune system priming with neoadjuvant PD-1 blockade compared with adjuvant therapy only. (A) Adjuvant PD-1 blockade after surgery: without neoadjuvant PD-1 blockade, nephrectomy can lead to decrease in PD-1 expression on all peripheral blood mononuclear cell types. Subsequent adjuvant administration of anti-PD-1 therapy elicits a response with antitumor T cells throughout the body including the tumor microenvironment, lymph node drainage, and distant sites. **(B)** Combined neoadjuvant and adjuvant PD-1 blockade with surgery: neoadjuvant PD-1 blockade primes the immune system prior to surgery when the tumor is in place resulting in proliferation of antitumor T cells prior to nephrectomy in the presence of tumor antigen. The response is augmented after nephrectomy by continued adjuvant PD-1 inhibition. Image adapted from: WikiJournal of Medicine Medical gallery of Blausen Medical 2014.

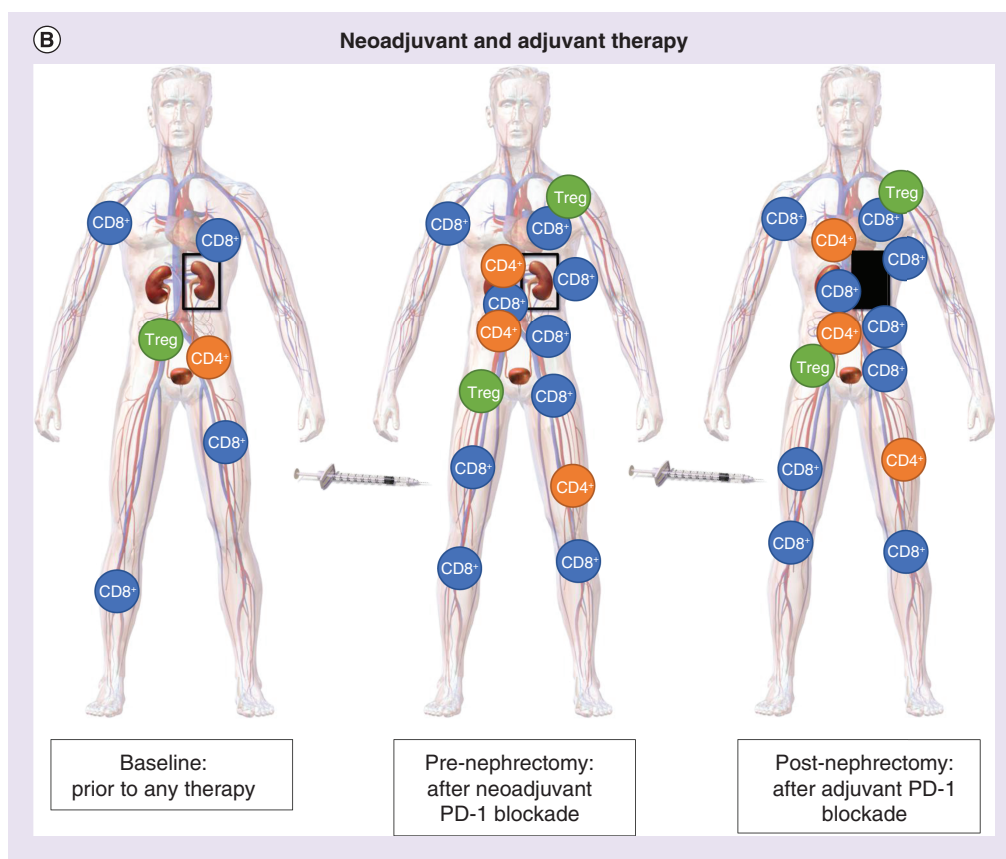


Figure 1. Schematic theoretic representation of the potential immune system priming with neoadjuvant PD-1 blockade compared with adjuvant therapy only (cont.). (A) Adjuvant PD-1 blockade after surgery: without neoadjuvant PD-1 blockade, nephrectomy can lead to decrease in PD-1 expression on all peripheral blood mononuclear cell types. Subsequent adjuvant administration of anti-PD-1 therapy elicits a response with antitumor T cells throughout the body including the tumor microenvironment, lymph node drainage, and distant sites. **(B)** Combined neoadjuvant and adjuvant PD-1 blockade with surgery: neoadjuvant PD-1 blockade primes the immune system prior to surgery when the tumor is in place resulting in proliferation of antitumor T cells prior to nephrectomy in the presence of tumor antigen. The response is augmented after nephrectomy by continued adjuvant PD-1 inhibition.

Image adapted from: WikiJournal of Medicine Medical gallery of Blausen Medical 2014.

faith effort, and patients do not need to undergo a second biopsy if otherwise consistent with RCC by imaging characteristics. **Box 1** provides further details on conditions and criteria leading to exclusion such as other current malignancies, certain autoimmune diseases, corticosteroid use restrictions, liver disease, serious intercurrent disease and hypersensitivity to monoclonal antibodies. Patients randomized to observation only after nephrectomy will be excluded from the primary analysis if there is evidence of non-RCC pathology.

Planned sample size

The planned sample size accounts for up to 5% of patients to have non-RCC pathology at time of nephrectomy leading to exclusion. Therefore, the total planned accrual is 805 patients to ensure that at least 766 patients with RCC will be randomized in a 1:1 fashion between the nivolumab and observation arms (383 per arm). Sample size calculations were based on the historical control cohort of ASSURE which had a RFS of 55.8% at 5-years and assumption that 10% of patients will either not undergo nephrectomy or not be disease-free after surgery [9]. Interim analyses and one-sided type 1 error rate of 2.5% for a stratified log-rank test are incorporated into calculations. The planned sample size will provide 84.2% power to detect an absolute difference in RFS of 14.4% or a planned increase from 55.8% in the observation arm to 70.2% in the nivolumab arm (HR: 0.70). For the clear cell RCC

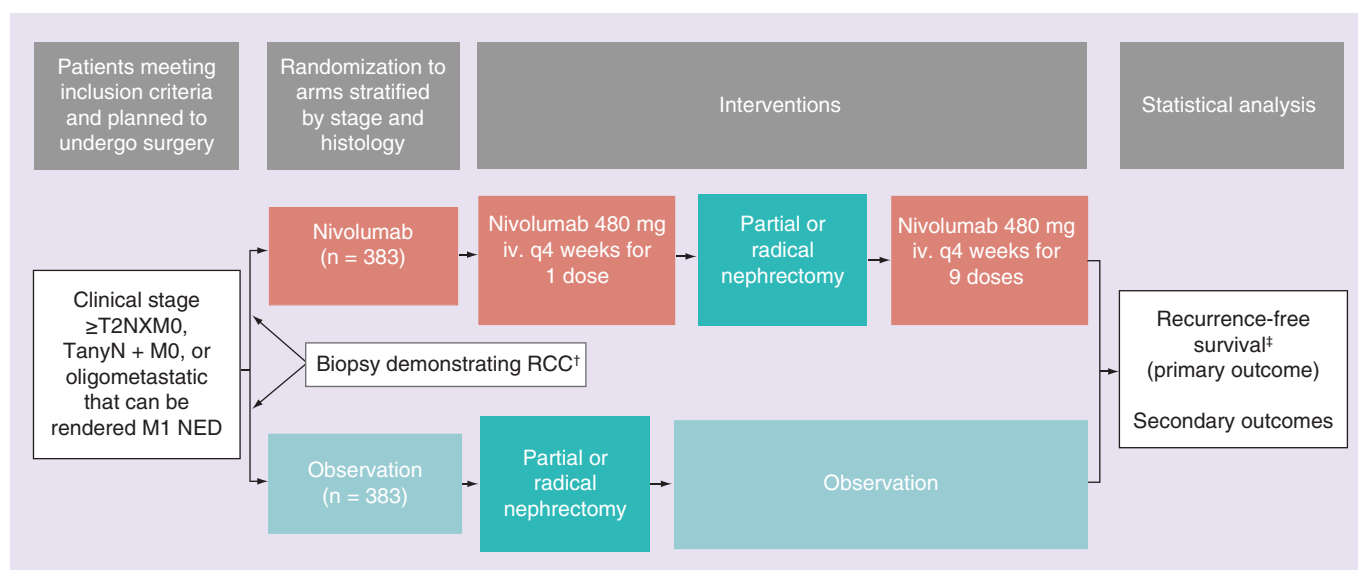


Figure 2. PROSPER renal cell carcinoma schema.

†Biopsy is mandated for patients assigned to the nivolumab arm. Biopsy is encouraged, but not mandated, for patients assigned to the observation arm. Management of oligometastatic disease can be done before or after nephrectomy as long as within a 12-week time frame.

‡The primary outcome is evaluated after exclusion of non-RCC surgical pathology.

iv.: Intravenous; RCC: Renal cell carcinoma.

subset, there is 82% power to detect a similar increase in RFS (13%; HR: 0.70). Additionally, there will be 80% power in the secondary end point of 5-year OS to detect an increase from 78.7 to 85.2% (HR: 0.67).

Study procedures

PROSPER RCC opened to enrollment on 2 February 2017 and is actively recruiting. Initially, patients assigned to the nivolumab arm received nivolumab 240 mg iv. every 2 weeks for two total doses followed by planned radical or partial nephrectomy at a minimum of 7 days but no more than 21 days after the last presurgical dose. Following surgery, patients received 12 adjuvant doses – 240 mg every 2 weeks for six doses then 480 mg every 4 weeks for six doses. To enhance quality of life and facilitate surgical scheduling, the protocol has been revised to transition all dosing to the 480 mg every 4 weeks schedule with only one neoadjuvant administration and a total of nine planned adjuvant doses (Figure 2). Patients assigned to the observation arm will proceed with planned radical or partial nephrectomy within 8 weeks after randomization. Patients with evidence of non-RCC surgical pathology will be excluded from the primary analysis.

All patients will undergo routine clinical postoperative surveillance with cross-sectional imaging at 20 weeks and 40 weeks after randomization followed by every 6 months through year 3 and then annually from years 4 to 10. Imaging studies will be banked to allow for potential blinded central review if deemed necessary and for future correlative studies in association with our ACRIN colleagues.

Outcome measures/end points

The primary end point is 5-year RFS defined as the interval from randomization (excluding patients with non-RCC surgical pathology) to the detection of disease recurrence or death with censoring at last follow-up for patients who have not recurred. After randomization, patients who do not receive surgery or with any evidence of continued disease after surgery will be analyzed as recurrence events occurring on day 1. Key secondary end points include OS for the entire cohort and RFS and OS in the clear cell RCC subset.

Safety and quality of life are important end points given the potential toxicity of PD-1 blockade. Quality of life will be assessed via the NCCN/FACT Kidney Symptom Index-19, PROMIS Physical Function 10-item short form, and nine questions from the PRO-CTCAE measuring patient-reported toxicity.

Imaging, pathology and serum samples are being collected for future correlative studies including assessment of clinical and pathologic biomarkers and predictive gene expression patterns. The planned tissue collection

Box 1. Key inclusion and exclusion criteria for PROSPER renal cell carcinoma.**Key inclusion criteria[†]**

- Age ≥ 18 years of age
- Clinical stage $\geq T2NX$ or TanyN+ disease; oligometastatic disease (≤ 3 sites of metastases) is permitted if planned to undergo local treatment of the metastases within 12 weeks of nephrectomy (metastasectomy, thermal ablation or stereotactic radiation)
- Preoperative biopsy demonstrating RCC within 4 months of randomization (if assigned to nivolumab arm) or suspicion of RCC (if assigned to observation arm with exclusion from primary analysis if non-RCC evidence on surgical pathology)
- Planned to undergo radical or partial nephrectomy; bilateral synchronous RCC is eligible only if the tumors can be resected at the same time with adequate residual renal function
- ECOG 0 or 1

Serum lab values within 4 weeks of randomization

- White blood cell count $\geq 2000/\mu\text{l}$
- Absolute granulocyte count $\geq 1.5/\text{mm}^3$
- Platelet count $\geq 100,000/\text{mm}^3$
- Hemoglobin ≥ 0.9 g/dl
- Cr $\leq 1.5 \times$ ULN or calculated creatinine clearance ≥ 40 ml/min
- Total bilirubin $\leq 1.5 \times$ ULN; $< 3.0 \times$ ULN for subjects with Gilbert syndrome
- AST and ALT $\leq 2.5 \times$ ULN

Key exclusion criteria[†]

- Concurrent or prior systemic or local anticancer therapy for RCC[‡]
- Prior history of RCC resected with curative intent within past 5 years
- Bilateral synchronous RCC requiring removal of both kidneys and subsequent hemodialysis
- Any metastasis to the liver, bone or central nervous system
- Most other current malignancies[§]
- Active or known autoimmune disease[¶]
- Ongoing condition requiring systemic corticosteroids or immunosuppressive medications[#]
- Uncontrolled adrenal insufficiency
- Known chronic active liver disease or acute/chronic hepatitis B or hepatitis C virus infection
- Serious intercurrent illness

[†]See NCT03055013 for full listing of eligibility criteria.

[‡]Examples include radical or partial nephrectomy for RCC, metastasectomy for RCC, radiation to the renal bed or distant metastatic sites, antineoplastic systemic therapy for RCC, and prior treatment with any antibody or drug targeting T-cell co-stimulation or checkpoint pathways (e.g., anti-PD-1, anti-PD-L1, anti-PD-L2, anti CD-137, anti-CTLA-4).

[§]The following exceptions are permitted: low-risk prostate cancer on active surveillance, adequately treated basal cell or squamous cell skin cancer, *in situ* cervical cancer, stage I or II cancer currently in complete remission, or any other cancer from which the patient has been disease-free ≥ 3 years prior to registration and not receiving any current treatment are allowed. A history of Ta urothelial cancer is permitted but not $\geq T1$ disease.

[¶]Except vitiligo, T1DM, asymptomatic or residual hypothyroidism that may require hormone replacement, psoriasis not requiring systemic treatment, and conditions not expected to recur.

[#]Except topical/ocular/intra-articular/intranasal/inhaled steroids or adrenal replacement in absence of active autoimmune disease; brief (< 3 week) course of corticosteroids for prophylaxis or treatment of nonautoimmune conditions is permitted if > 14 days since last dose.

ALT: Alanine aminotransferase; AST: Aspartate aminotransferase; Cr: Creatinine; ECOG: Eastern Cooperative Oncology Group; RCC: Renal cell carcinoma; ULN: Upper limit of normal.

will provide high quality data on clinical stage, biopsy pathology, surgical pathology, serologic immune changes and longitudinal outcomes. The captured data and tissue may also help clarify outstanding questions related to predicting outcomes by stage, utility of preoperative renal biopsy for risk-stratification and identifying predictive biomarkers [30,34]. The impact of priming on the primary tumor due to neoadjuvant nivolumab will be assessed by evidence of trafficking and proliferation of CD8-positive T cells. The effects of baseline and changes in PD-L1 expression on outcomes will be assessed. Banking of imaging studies may support studies aimed at characterizing the presence and severity of cancer such as with breast or prostate cancers (BI-RADS, PIRADS; now Ki-RADs) [35]. Genomic analyses will sequence the exome and transcriptome for mutational and neoantigen loads as well as pathway activation for correlation with outcomes. Both gene expression patterns and cytokine signatures will be explored. In addition, a planned substudy will generate patient RCC organoids to characterize *in vitro* and *in vivo* growth rates, histopathology and immunohistochemistry for comparison with the original RCC tumor sample.

Statistical considerations

Patients with evidence of non-RCC at the time of surgical pathology review will be excluded from the primary analysis. Baseline data on demographics and clinical stage will be tabulated by arm. Descriptive statistics will note median follow-up, adherence to frequency of follow-up imaging and the proportion of patients that deviated from the protocol in either arm (e.g., did not undergo surgery or receive the full course of nivolumab). Intent-to-treat analyses will employ a stratified log-rank test and derive comparative effect measures (HRs). Survival curves will be generated for the planned survival outcomes. Although every effort will be made to obtain scans at the scheduled time points, sensitivity analyses will be employed by carrying forward dates of events detected at nonscan visits and comparing the proportion alive and recurrence-free at the 27-month postrandomization scan.

The frequency and type of adverse events will be graded and reported by arm. A Data Safety Monitoring Committee will regularly review safety data from first enrollment through release for analysis and may recommend stopping the study for harm at 25% information if the lower bound of the 95% CI from the nivolumab/observation HR is above 1.0. Futility monitoring will begin at 44% information.

Correlative and exploratory analyses will stratify patient subsets based on pathologic variables including histology for the outcome of RFS. The primary quality of life analysis will be performed after the 40-week follow-up forms have been completed, and then a second planned analysis will occur when all patients have completed the 2-year forms.

Conclusion

Despite surgical resection, up to 45% of patients with high-risk RCC may recur and over 20% of those patients die within 5 years. There has been subdued enthusiasm for adopting adjuvant antiangiogenic therapies given the trade-off between high adverse event profiles and debatable clinical benefit. PD-1 blockade via modern monoclonal antibodies has emerged as an effective disease-modifying treatment for metastatic RCC with preclinical evidence and early stage trials in other solid tumors supporting a potential role in the locally advanced setting, especially when given neoadjuvantly. PROSPER RCC is unique among the ongoing Phase III adjuvant trials by employing a neoadjuvant component to prime the immune system with PD-1 blockade prior to surgery. The presurgical dosing will also permit highly translational correlative work capitalizing on the availability of pre- and postnivolumab treated tissue and sera with rigorous contemporary control tissue from the observation arm. The study is powered to assess clinically meaningful end points of RFS and OS and if positive, will dramatically shift the treatment paradigm for high-risk RCC.

Executive summary

Background

- Patients with high-risk renal cell carcinoma (RCC) experience high rates of recurrence despite definitive surgical resection. Recent trials of adjuvant tyrosine kinase inhibitor therapy show conflicting efficacy results and that administration comes at the cost of significant rates of toxicity and intolerability with no definite impact on overall survival. PD-1 blockade via monoclonal antibodies has emerged as an effective disease-modifying treatment for metastatic RCC with preclinical evidence supporting a potential role in the locally advanced setting.

The Trial: PROSPER RCC

- A Phase III, nonplacebo controlled randomized trial designed to evaluate the impact of perioperative nivolumab compared with observation on recurrence-free survival in 805 patients undergoing nephrectomy for high-risk RCC.

Objectives

- PROSPER RCC will provide the first comparative data on a three-pronged approach to improve outcomes for high-risk RCC by employing both neoadjuvant and adjuvant therapy with the PD-1 inhibitor nivolumab in addition to standard of care nephrectomy.
- The primary objective is to improve recurrence free survival.
- Key secondary objectives are to increase overall survival and quality of life as well as ensure safety and tolerability.
- The neoadjuvant administration of nivolumab is intended to prime the immune system when the majority of the tumor antigen is in place to induce a more robust antitumor response.
- A wealth of correlative science has been tightly integrated into the study given the unique availability of pre- and postnivolumab tumor tissue and sera which provides a major opportunity for biomarker discovery.

Supplementary data

An infographic accompanies this paper at the end of the references section. To download the infographic that accompanies this paper, please visit the journal website at: www.futuremedicine.com/doi/full/10.2217/fo-2018-0951

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Trial registration

This study was registered on ClinicalTrials.gov (NCT03055013) as well as SWOG (CTSU/EA8143).

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