

## Review Article

# Current Status of Immunotherapy for Localized and Locally Advanced Renal Cell Carcinoma

Fady Ghali, Sunil H. Patel, and Ithaar H. Derweesh 

Department of Urology UC San Diego School of Medicine, La Jolla, California, USA

Correspondence should be addressed to Ithaar H. Derweesh; [iderweesh@gmail.com](mailto:iderweesh@gmail.com)

Received 29 December 2018; Revised 26 February 2019; Accepted 11 March 2019; Published 1 April 2019

Guest Editor: Aditya B. Pant

Copyright © 2019 Fady Ghali et al. This is an open access article distributed under the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

Systemic therapy strategies in the setting of localized and locally advanced renal cell carcinoma (RCC) have continued to evolve in two directions: as adjuvant therapy (to reduce risk of recurrence or progression in high risk localized groups), or as neoadjuvant therapy as a strategy to render primary renal tumors amenable to planned surgical resection in settings where radical resection or nephron-sparing surgery was not thought to be safe or feasible. In the realm of adjuvant therapy, the results of phase III randomized clinical trials have been mixed and contradictory; nonetheless based on the findings of the landmark S-TRAC study, the tyrosine kinase inhibitor Sunitinib has been approved as an adjuvant agent in the United States. In the realm of neoadjuvant therapy, presurgical tumor reduction has been demonstrated in a number of phase II studies utilizing targeted molecular agents. The advent of immunomodulation through checkpoint inhibition as first line therapy for metastatic RCC represents an exciting horizon for adjuvant and neoadjuvant strategies. This article reviews the current status and future prospects of adjuvant and neoadjuvant immunotherapy in localized and locally advanced RCC.

## 1. Introduction

Renal Cell Carcinoma (RCC) is common cancer globally, with approximately 400,000 people being diagnosed with RCC in 2018, a notable increase in incidence rates with time, and is among the top ten most common malignancies in the United States [1, 2]. Due to the widespread use of cross-sectional imaging, incidence of RCC has increased with most cases presenting as localized disease [3–5]. Despite such stage migration, the risk of recurrence remains high [6–9]. Poor prognosis of patients with recurrence and the risks associated with locally advanced resection or nephron-sparing surgery in the imperative setting for complex masses have served as an impetus to explore further approaches to improve outcomes.

The improved response rates and outcome in metastatic RCC ushered in the era of targeted therapies; both tyrosine kinase inhibitor (TKI) therapy and immune checkpoint inhibitors (ICI) have stimulated investigation into the utility of these agents as adjuvants in the setting of localized and locally advanced disease to reduce the risk of recurrence and improve survival [10–15]. Herein, we review and summarize the current status and future directions of adjuvant and

neoadjuvant immunotherapeutic strategies in localized and locally advanced RCC, focusing on current literature and ongoing clinical trials in both areas.

## 2. Methodology

**2.1. Literature Search.** PubMed, MEDLINE, Cochrane Central Register of Controlled Trials, the American Society of Clinical Oncology, and ClinicalTrials.gov were searched with keywords including “neoadjuvant”, “adjuvant”, “immunotherapy”, “targeted therapy”, “immune checkpoint (anti-PD-1) inhibitors”, and “renal cell carcinoma”. Publications were included in the review if they were including patients with localized RCC. Articles other than English language, editorials, and case reports were excluded.

**2.2. Assessment of Response.** In adjuvant therapeutic investigations, survival endpoints included overall survival (OS), disease-free survival (DFS), and recurrence-free survival (RFS). These terms are defined as the interval of time from randomization to the first recurrence (locally or at distant

TABLE 1: Clinical criteria for adjuvant therapy or investigations and neoadjuvant therapeutic investigations.

| Adjuvant Therapy         | Neoadjuvant Therapy                  |
|--------------------------|--------------------------------------|
| Resected primary tumor   | T1-4 NX/1 M0                         |
| and                      | or                                   |
| pT2-3 N0 M0 (grades 2-4) | T1-4 NX/1 M1                         |
| or                       | or                                   |
| pT4 N0 M0                | Borderline resectable mass           |
| or                       | or                                   |
| pTany N1 M0              | Facilitating nephron-sparing surgery |
|                          | or                                   |
|                          | Downstaging IVC thrombus             |

metastatic sites), or the occurrence of secondary malignancies or death, and are generally used interchangeably [16]. Early investigations tended to focus on RFS as an endpoint, with more recent studies focusing on OS as the primary endpoint [17]. To assess tumor response in neoadjuvant investigations a number of criteria have been utilized to evaluate therapeutic effect: change in tumor size measured in greatest diameter, 2-dimensional product of tumor cross section based on cross-sectional imaging (WHO criteria) [18], Response Evaluation Criteria In Solid Tumors (RECIST) criteria [which defined partial response (PR) as  $\geq 30\%$  reduction in the primary lesion size, progressive disease (PD) as increase in tumor size  $\geq 20\%$  or presence of new lesions or stable disease (SD)] [19], and changes in tumor morphometric score, such as the RENAL (Radius Exophytic Nearness Anterior Location) nephrometry score, a system used for defining tumor complexity [20]. Table 1 demonstrates clinical criteria in which adjuvant and neoadjuvant agents have been investigated. In the adjuvant realm, these have been resected primary tumor and pT2-3 N0 M0 (grades 2-4), pT4 N0 M0, or pTany N1 M0. In the neoadjuvant realm, these are T1-4 NX/1 M0, T1-4 NX/1 M1, borderline resectable masses, facilitation of nephron-sparing surgery, or downstaging IVC thrombi resections.

### 3. Adjuvant Immunotherapy in the Management of Localized and Locally Advanced Renal Cell Carcinoma

In the TKI era, significant investigational efforts were conducted into the utility of these agents as adjuvants after extirpative surgery to reduce risk of recurrence and improve survival, with mixed and largely negative results. A summary of TKI trials is provided in Table 2. The first of these pivotal trials was the ASSURE trial (Adjuvant Sorafenib or Sunitinib in Unfavorable Resected Renal cancer) which enrolled 1943 patients with nonmetastatic high risk RCC with a study design to randomize according to a 1:1:1 ratio to receive Sunitinib 50mg, Sorafenib 800mg, or placebo for 1 year with a primary endpoint of DFS. The study ultimately found no difference in DFS between groups (HR 1.02, 97.5% CI 0.85-1.23) and was hampered by high rates of toxicity and discontinuation in the two treatment arms [36]. The

PROTECT trial, which examined two doses of Pazopanib versus placebo, found a marginal benefit in DFS on secondary analysis in those patients receiving higher dose (800mg, HR 0.69 [95% CI 0.51-0.94 p=0.02]), and no difference in the lower dose group [37]. The ATLAS trial compared Axitinib with placebo randomizing 724 patients. The study was closed due to futility as there was no significant difference in DFS (HR=0.87; 95% CI: 0.660-1.147, p=0.321) overall [24]. It was the S-TRAC (Sunitinib Treatment of Renal Adjuvant Cancer) trial that was the first to show a significant improvement in DFS with this class of medications. A total of 615 high risk nonmetastatic patients were randomized to Sunitinib 50mg vs Placebo with a median follow up of 5.4 years. The study demonstrated an improved DFS of 6.8 v 5.6 years, HR 0.76, 95% CI 0.59-0.95, p=0.03. In this, like all the other studies, the toxicity associated with this class of medications was notable, as high as 60.5% [38].

Based on results of the S-TRAC study demonstrating a benefit in DFS, the United States Food and Drug Administration (FDA) approved Sunitinib as an adjuvant agent for high risk localized RCC in November 2017, the first such agent in RCC [15]. Indeed, regulatory approval has heralded a paradigm shift, which has been reflected in the recently updated NCCN guidelines that lists adjuvant therapy with Sunitinib as an option for patients with stage III disease, clear cell histology, and high risk for recurrence [39]. Still, there exist concerns regarding the reproducibility and relatively modest clinical benefit associated with TKI. In February 2018, for example, the European Medicines Agency rejected the use of Sunitinib in the adjuvant setting for high risk localized RCC for these reasons [29]. Nonetheless, enrollment in a clinical trial is still considered a preferred option for most patients at higher risk for recurrence after complete resection for localized RCC.

**3.1. Immune Checkpoint Inhibitors.** The emergence and success of immune checkpoint inhibition as a front-line therapeutic strategy for metastatic RCC has also heralded investigation of these agents as potential adjuvant agents [13, 40]. Indeed, the biologic rationale for immunotherapeutic adjuvant therapy is compelling, and perhaps more so than for TKI agents from a mechanistic standpoint. Clearance of circulating tumor cells or micrometastatic deposits by enhancement of the T1 immune tumor response by blockade of programmed death (PD)-1 receptor and programmed death-ligand 1 (PDL-1) may represent a more efficacious therapeutic pathway that antiangiogenic blockade [21], as has been demonstrated in management of clinical metastatic disease [13, 22]. Currently there are 4 clinical trials examining the potential of checkpoint inhibitors in localized RCC to reduce risk of recurrence: atezolizumab (1 trial, NCT03024996) [40], combination of nivolumab and ipilimumab (1 trial, NCT03138512) [23], pembrolizumab (1 trial, NCT03142334) [30], and durvalumab monotherapy or in combination with tremelimumab (NCT03288532) [41] (summarized in Table 3).

The IMmotion010 trial randomizes resected high risk clear cell or sarcomatoid RCC (pT3a+, high grade including M1 resected disease) to atezolizumab (PDL1 inhibitor) or placebo. The primary end point is RFS determined by

TABLE 2: Summary of adjuvant trials: completed and reported.

| Trial                                  | Design   | Intervention           | N    | Inclusion Criteria (stage/grade/histology)   | Results  | Adverse Events  |
|--|--|------------------------|------|--|--|---|
| ASSURE, Haas et al. (2016) [21]        | Randomized, Double-blinded, Placebo-controlled | Sunitinib or Sorafenib | 1943 | T1b N0 M0 (grade 3-4), pT2-pT4 N0 M0, pT(any) N1 M0; Clear Cell and Non-clear Cell | No difference in median DFS (HR 1.02, 97.5% CI 0.85-1.23)        | Grade 3+ toxicities of sunitinib, sorafenib: hypertension (17%, 16%), hand-foot syndrome (15%, 33%), rash (2%, 15%), fatigue (18%, 7%)<br>Increased ALT/AST lead to treatment discontinuation in 600 mg (ALT 16%/AST 5%) and 800 mg (ALT 18%/AST 7%) mg.<br>Similar and serious adverse events between groups; more grade 3/4 (61% vs. 30%) for axitinib<br>Increased Grade 3 (48.4% vs. 15.8%); Grade 4 (12.1% vs. 3.6%) in sunitinib; Similar serious event rate. |
| PROTECT, Motzer et al. (2017) [22]     | Randomized, Double-blinded, Placebo-controlled | Pazopanib              | 1538 | pT2 N0 M0 (grades 3-4), pT3-4 N0 M0, pT(any) N1 M0; Clear Cell                     | No differences in median DFS (HR 0.86, 95% CI 0.70-1.06)         |   |
| ATLAS, Gross-Goupil et al. (2018) [23] | Randomized, Double-blinded, Placebo-controlled | Axitinib               | 724  | pT2-4 N0 M0, pT(any) N1 M0; Clear Cell   | No difference in median DFS (HR 0.87, 95% CI 0.66-1.15, p=0.321) |   |
| S-TRAC, Ravaud et al. (2016) [24]      | Randomized, Double-blinded, Placebo-controlled | Sunitinib              | 615  | pT3 N0 M0 (grades 2-4), pT4 N0 M0, pT(any) N1 M0; Clear Cell                       | Improved median DFS (6.8 years v 5.6; HR 0.76, 95% CI 0.59-0.98) |   |

TABLE 3: Summary of adjuvant and neoadjuvant immunotherapeutic trials: completed and reported.

| Trial                             | Design   | Intervention   | N   | Inclusion Criteria (stage/grade/histology)                  | Results   | Adverse Events   |
|-----------------------------------|--|--|-----|---|---|--|
| Adjuvant Trials                   |  |  |     |   |   |  |
| Jocham et al. (2004) [25]         | Prospective, randomized                        | Autologous renal tumor cells                                     | 558 | pT2-3b pN0-3 M0; Clear and Non-Clear Cell                   | Improved 5 year and 70 month PFS (HR 1.58, 95% CI 1.05-2.37; HR 1.59, 95% CI 1.07-2.36) | Local skin reactions   |
| Wood et al. (2008) [26]           | Prospective, randomized                        | Autologous tumor-derived protein                                 | 819 | cT1b-4 N0 M0, cT(any) N1-2 M0; Clear and Non-Clear Cell     | No difference in PFS at 1.9 median year follow-up (HR 0.92, 95% CI 0.729-1.169)         | Local skin reactions   |
| ARISER, Chamie et al. (2016) [27] | Randomized, Double-blinded, Placebo-controlled | Girentuximab   | 864 | pT1b-2 (Fuhrman $\geq$ 3), pT3-4 N0, pT(any) N+; Clear Cell | No difference in DFS (HR 0.97, 95% CI 0.79-1.18) or OS (HR 0.99, 95% CI 0.74-1.32)      | Toxicity rate 21%, comparable to placebo                                     |
| Neoadjuvant Trial                 |  |  |     |   |   |  |
| Cost et al (2011) [28]            | Retrospective                                  | Sunitinib (12), bevacizumab (9), sorafenib (1), temsirolimus (3) | 25  | T3b+M1 (21)   | 25/0  | 12% downstage thrombus level; 4% upstage level; 4% altered surgical strategy |

central radiologic assessment [40]. Checkmate-914 is a trial enrolling patients to a combination PD1 inhibitor + CTLA4 inhibitor (nivolumab with ipilimumab) or placebo for high risk clear cell RCC [23]. Keynote-564 is enrolling patient for adjuvant pembrolizumab (PD1 inhibitor) verses placebo for high risk patients with clear cell histology including M1

resected disease [30]. The RAMPART study recently began enrolling clear and nonclear cell patients to one of three arms: durvalumab with tremelimumab (PDL1 inhibitor + CTLA4 inhibitor), or durvalumab monotherapy, or placebo [41]. Current immunotherapeutic ongoing studies in the adjuvant setting are summarized in Table 4.

TABLE 4: Summary of adjuvant and neoadjuvant studies: ongoing or unreported.

| Trial   | Design   | Agent  | Planned Accrual | Inclusion Criteria (stage/grade)  | Inclusion Criteria (histology) |
|---|--|--|-----------------|---|--------------------------------|
| <b>Adjuvant Trials</b>                              |  |  |                 |   |                                |
| IMmotion010, (NCT03024996) [29]                     | Prospective, double-blinded, placebo controlled              | Atezolizumab                                 | 664             | Nonmetastatic   | Clear cell, sarcomatoid        |
| Checkmate-914, (NCT03138512) [22]                   | Prospective, double-blinded, placebo controlled              | Nivolumab + Ipilimumab                       | 800             | pT2a – 4 N0 M0 (any), pT1-4 N1 M0 (any)   | Clear cell                     |
| Keynote-564, (NCT03142334) [23]                     | Prospective, double-blinded, placebo controlled              | Pembrolizumab                                | 950             | pT2 N0 M0 (grade 4 or sarcomatoid), pT3-4 N0 M0 (any), pT1-4 N1 M0, Resectable M1 | Clear cell                     |
| RAMPART, (NCT03288532) [30]                         | Prospective, multicenter, double-blinded, placebo controlled | Durvalumab, Durvalumab + tremelimumab        | 1750            | Leibovich Score 3-11  | Any                            |
| <b>Neoadjuvant Trials</b>                           |  |  |                 |   |                                |
| Merck Sharp Dohme Corp (NCT02212730) [31]           | Prospective, open label, parallel assignment                 | Pembrolizumab                                | 36              | cT1b+ NX-0 M0   | Any                            |
| Bristol-Myers Squibb (NCT02575222) [32]             | Prospective, open label                                      | Nivolumab                                    | 30              | cT2a-T4 NX-1 M0, cT1-4 N1 M0  | Clear cell                     |
| NCI (NCT02595918) [33]                              | Prospective, open label                                      | Nivolumab                                    | 29              | Stage I-III   | Clear cell                     |
| Case Comprehensive Cancer Center (NCT02762006) [34] | Prospective, open label                                      | Durvalumab, Tremelimumab                     | 45              | cT2b-4 NX-0 M0 cT1-4 N1, M0   | Any                            |
| PROSPER, (NCT03055013) [35]                         | Randomized, double-blind, placebo controlled                 | Nivolumab                                    | 766             | cT2 NX M0, cT1-4 N1 M0  | Any                            |
| Roswell Park Cancer Institute (NCT02170389) [31]    | Prospective, open label                                      | RCC/CD40L RNA-Transfected Autologous Vaccine | 4               | pT1, NX-0, M0   | Any                            |

#### 4. Vaccines and Targeted Immunotherapy

Tumor vaccines and targeted immunotherapy have been investigated in the adjuvant setting for RCC. This concept was first explored by Galligioni et al., which utilized autologous tumor cells and bacillus Calmette-Guerin, with negative results [25]. Variations on the same theme have been attempted with the same result [26, 27]. Jocham et al. published results of a randomized trial in 379 patients with pT2-3b N0-3 RCC to receive autologous renal tumor cell vaccine or no treatment and demonstrated decreased tumor progression in the treatment group at 5 years (HR 1.59, CI 1.07 – 2.36,  $p = 0.0304$ ) [26]. More recently, in the ARISER study, girentuximab, a chimeric antibody targeting

carbonic anhydrase IX (CAIX), was evaluated as adjuvant in 864 patients with high risk RCC. Girentuximab was well-tolerated, with toxicity rates comparable to placebo. Overall however, there was no significant difference between girentuximab and placebo for DFS (HR 0.97, 95% CI 0.79–1.18) or OS (HR 0.99, 95% CI 0.74–1.32) [42].

#### 5. Neoadjuvant Therapy in Clinically Localized and Locally Advanced Renal Cell Carcinoma

Neoadjuvant therapy for RCC was initially implemented to accomplish reduction in metastatic disease prior to surgical debulking, facilitate more complex surgical resections, and

select patients with appropriate disease response to systemic therapy who may benefit from surgical debulking (Table 1) [43, 44]. Indeed, the paradigm of presurgical or primary systemic therapy in the setting of metastatic RCC for TKI has recently been solidified by publication of the SURTIME and CARMENA studies which suggested improvements in PFS with primary TKI prior to surgery and lack of improvement of outcomes in intermediate and high risk metastatic RCC in patients receiving primary cytoreductive nephrectomy, respectively [45, 46]. There have been 15 studies reported in the literature for indications of downstaging tumor size for resection of locally advanced disease (9 studies), facilitating partial nephrectomy (5 studies), and downstaging IVC thrombus level (4 studies). The first study assessing feasibility and efficacy of neoadjuvant therapy prior to resection of locally advanced disease was conducted by Thomas et al. who examined 19 patients with locally extensive primary tumors considered otherwise unresectable were administered Sunitinib (initial dose 50 mg daily) for one 4-week cycle. Analysis noted partial response in 16% (3/19) of patients (by RECIST criteria) with median size reduction of 24% and with 21% (4/19) eventually undergoing nephrectomy. Nonetheless, the authors also reported that 37% of patients experienced grade 3-4 toxicities. No unexpected surgical morbidity was found; however, the major complication rate was not reported [44]. Since then, others that have studied this outcome with various other TKIs have observed 11.8%-28% median reduction in tumor size. In the first prospective randomized double-blind placebo-controlled trial to assess downsizing effect of neoadjuvant TKI, Hatiboglu et al. randomized 12 patients in a 3:1 manner to sorafenib vs placebo and demonstrated median tumor volume reduction of 29% in the treatment group. Nonetheless, toxicity rates are significant as are high grade complications [47-50].

Another indication for investigation into the utility of neoadjuvant therapy has been to facilitate nephron-sparing surgery. The first study to focus on this particular aim was reported by Silberstein et al., who conducted a prospective pilot study and a retrospective multicenter review analyzing outcomes of neoadjuvant Sunitinib (50 mg daily for two 6-week cycles) in 12 patients (14 tumors) with clear cell RCC who had imperative indications for nephron-sparing surgery. The authors noted a mean tumor size reduction of 21.1% (7.1 to 5.6 cm) with 4/14 (28.6%) tumors having PR by RECIST criteria. Ultimately, partial nephrectomy was achievable in all patients without positive margins or requirement for dialysis. Nonetheless, the authors reported that 3/14 (21.4%) renal units experienced urine leaks, all of which resolved with conservative measures [51].

Others have studied the role of various other TKIs in facilitating nephron-sparing surgery and have had mixed results. Taken together the body of work in this area suggests that neoadjuvant TKI therapy for locally advanced disease or prior to partial nephrectomy may result in modest decreases in tumor size and complexity in a subset of patients; partial nephrectomy in this setting remains complex and requires surgical expertise in this area [28, 34, 35, 44, 50-56].

## 6. Neoadjuvant Therapy in the Management of Localized RCC: Future Directions

Similar to the advent of immunotherapeutic investigation for adjuvant therapy in localized RCC, a flurry of high quality studies are currently underway to examine the role of neoadjuvant ICI or combination ICI-TKI targeted therapy for advanced disease, particularly in the wake of the first positive trial demonstrating improved PFS using combination TKI and immune checkpoint inhibitors compared to TKI alone (13.8 vs 7.2 months PFS and response rate of 55.2% vs 25.5% favoring combination therapy) [31]. Currently, seven clinical trials in this arena are ongoing and are summarized in Table 4. Of these studies, 4 involve immune checkpoint inhibitors.

The anti-PD-1 receptor antibody pembrolizumab (1 study; NCT02212730) is currently enrolling (planned accrual of 36 patients) with any RCC histology and clinical cT1b or more, NX-0, M0 disease in a prospective, open label, parallel design [32]. Nivolumab, an anti-PD-1 receptor antibody, is also being studied in the neoadjuvant setting in both clear cell histology and any histology, in several ongoing prospective trials, open label trials, and one randomized double-blind placebo-controlled trial (NCT02575222, NCT02595918, NCT03055013) [33, 57, 58]. Yet another clinical trial involves an antibody directed against programmed cell death-1 ligand 1 (durvalumab/MEDI 4736) ± tremelimumab, an antibody directed against human T-cell receptor protein cytotoxic T-lymphocyte-associated protein 4 (CTLA4). This study is investigating patients with any RCC histology and local or locally advanced disease in a prospective, open label fashion [59]. Finally, an additional clinical trial that evaluated presurgical vaccine therapy was closed after enrolling 4 patients (NCT02170389); further investigation in this region is pending [60].

Utilization of systemic therapy to promote cytoreduction of primary tumors and to facilitate surgical excision should currently be considered to be investigational. Nonetheless, this concept has been borne out in a number of prospective phase II studies [50, 52, 53] and retrospective analyses [54]. The key question, of course, is whether primary systemic therapy facilitates planned surgical intervention that would otherwise not have been feasible. Rini et al. suggested that the partial nephrectomy rate in otherwise unfeasible nephron-sparing situations was 75% [53] and the senior author of the manuscript is the study chair of the largest study to date which will test the question of neoadjuvant therapy prior to imperative indication partial nephrectomy in situations where a partial nephrectomy is not otherwise suitable [61].

A counter argument is often made which is due to variability of surgeon experience and ability, what may be considered unfeasible by one surgeon may indeed be possible and safe by another. While we agree in the validity of this criticism, there nonetheless exists a subset of patients in whom a safe and efficacious nephron-sparing procedure or locally advanced resection is truly not be feasible, and with even mild cytoreduction, feasibility and efficacy of such a resection may be enhanced. The senior author of this manuscript bases his opinion on the fact that he has one of the largest series in the literature of large partial nephrectomies

(>7cm) performed, whether by open approach [62, 63] or by minimally invasive approach [64]. We recently also demonstrated efficacy of primary systemic therapy prior to nephrectomy with IVC thrombectomy [65] and believe that our results and those emerging from other groups suggest that concept of primary cytoreductive systemic therapy has merit should be investigated further.

## 7. Conclusion

Utility and efficacy of systemic therapy in the setting of localized and locally advanced RCC are areas of active investigation. Recent approval of Sunitinib as an adjuvant agent has changed the paradigm of management of patients in the United States, and advent of ICI therapy as first line agents for metastatic RCC is spurring further investigation into utility of immunotherapeutic agents or combinations in adjuvant and neoadjuvant settings.

## Conflicts of Interest

Dr. Derweesh has received grant and investigational funding from Pfizer, Inc.

## Acknowledgments

This paper received Stephen Weissman Kidney Cancer Research Fund.

## References

- [1] F. Bray, J. Ferlay, I. Soerjomataram, R. L. Siegel, L. A. Torre, and A. Jemal, "Global Cancer Statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries," *CA: A Cancer Journal for Clinicians*, pp. 394–424, 2018.
- [2] R. L. Siegel, K. D. Miller, and A. Jemal, "Cancer statistics, 2016," *CA: A Cancer Journal for Clinicians*, vol. 66, no. 1, pp. 7–30, 2016.
- [3] D. C. Miller, J. Ruterbusch, J. S. Colt et al., "Contemporary Clinical Epidemiology of Renal Cell Carcinoma: Insight From a Population Based Case-Control Study," *The Journal of Urology*, vol. 184, no. 6, pp. 2254–2258, 2010.
- [4] W.-H. Chow, L. M. Dong, and S. S. Devesa, "Epidemiology and risk factors for kidney cancer," *Nature Reviews Urology*, vol. 7, no. 5, pp. 245–257, 2010.
- [5] C. J. Kane, K. Mallin, J. Ritchey, M. R. Cooperberg, and P. R. Carroll, "Renal cell cancer stage migration: analysis of the National Cancer Data Base," *Cancer*, vol. 113, no. 1, pp. 78–83, 2008.
- [6] J. M. Speed, Q.-D. Trinh, and T. K. Choueiri, "Recurrence in localized renal cell carcinoma: a systematic review of contemporary data," *Current Urology Reports*, vol. 18, no. 15, 2017.
- [7] S. Dabestani, A. Thorstenson, P. Lindblad, U. Harmenberg, B. Ljungberg, and S. Lundstam, "Renal cell carcinoma recurrences and metastases in primary non-metastatic patients: a population-based study," *World Journal of Urology*, vol. 34, no. 8, pp. 1081–1086, 2016.
- [8] M. Sorbellini, M. W. Kattan, M. E. Snyder et al., "A postoperative prognostic nomogram predicting recurrence for patients with conventional clear cell renal cell carcinoma," *The Journal of Urology*, vol. 173, no. 1, pp. 48–51, 2005.
- [9] A. Zisman, A. J. Pantuck, J. Wieder et al., "Risk Group Assessment and Clinical Outcome Algorithm to Predict the Natural History of Patients With Surgically Resected Renal Cell Carcinoma," *Journal of Clinical Oncology*, vol. 20, no. 23, pp. 4559–4566, 2002.
- [10] M. W. Ball, E. A. Singer, and R. Srinivasan, "Renal cell carcinoma," *Current Opinion in Oncology*, vol. 29, no. 3, pp. 201–209, 2017.
- [11] A. A. Lalani, B. A. McGregor, L. Albiges et al., "Systemic treatment of metastatic clear cell renal cell carcinoma in 2018: current paradigms, use of immunotherapy, and future directions," *European Urology*, vol. 75, pp. 100–110, 2018.
- [12] M. Atkins, J. Clark, and D. Quinn, "Immune checkpoint inhibitors in advanced renal cell carcinoma: experience to date and future directions," *Annals of Oncology*, 2017.
- [13] H. J. Hammers, E. R. Plimack, J. R. Infante et al., "Safety and Efficacy of Nivolumab in Combination With Ipilimumab in Metastatic Renal Cell Carcinoma: The CheckMate 016 Study," *Journal of Clinical Oncology*, vol. 35, no. 34, pp. 3851–3858, 2017.
- [14] C. M. Tobert, R. G. Uzzo, C. G. Wood, and B. R. Lane, "Adjuvant and neoadjuvant therapy for renal cell carcinoma: A survey of the Society of Urologic Oncology," *Urologic Oncology: Seminars and Original Investigations*, vol. 31, no. 7, pp. 1316–1320, 2013.
- [15] U. S. Food, *FDA Expands Approval of Sutent to Reduce the Risk of Kidney Cancer Returning*, U.S. Food & Drug Administration, 2017.
- [16] M. K. Wilson, K. Karakasis, and A. M. Oza, "Outcomes and endpoints in trials of cancer treatment: the past, present, and future," *The Lancet Oncology*, vol. 16, no. 1, pp. e32–e42, 2015.
- [17] E. A. Singer, G. N. Gupta, and R. Srinivasan, "Update on targeted therapies for clear cell renal cell carcinoma," *Current Opinion in Oncology*, vol. 23, no. 3, pp. 283–289, 2011.
- [18] P. Therasse, S. G. Arbuuck, E. A. Eisenhauer et al., "New guidelines to evaluate the response to treatment in solid tumors," *Journal of the National Cancer Institute*, vol. 92, pp. 205–216, 2000.
- [19] E. A. Eisenhauer, P. Therasse, J. Bogaerts et al., "New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1)," *European Journal of Cancer*, vol. 45, no. 2, pp. 228–247, 2009.
- [20] S. P. Stroup, K. Palazzi, R. P. Kopp et al., "RENAL Nephrometry Score is Associated With Operative Approach for Partial Nephrectomy and Urine Leak," *Urology*, vol. 80, no. 1, pp. 151–156, 2012.
- [21] T. Zhang, J. Zhu, D. J. George, and A. B. Nixon, "Metastatic clear cell renal cell carcinoma: Circulating biomarkers to guide antiangiogenic and immune therapies," *Urologic Oncology: Seminars and Original Investigations*, vol. 34, no. 11, pp. 510–518, 2016.
- [22] R. J. Motzer, B. Escudier, D. F. McDerrmott et al., "NIVOLUMAB - CHECKMATE-025 TRIAL: nivolumab versus everolimus in advanced renal-cell carcinoma," *The New England Journal of Medicine*, vol. 373, pp. 1803–1813, 2015.
- [23] B. Squibb, "A phase 3 randomized study comparing nivolumab and ipilimumab combination vs placebo in participants with localized renal cell carcinoma who underwent radical or partial nephrectomy and who are at high risk of relapse," National Library of Medicine (US), Bethesda, Md, USA, 2000, <https://clinicaltrials.gov/ct2/show/NCT03138512>.

- [24] M. Gross-Goupil, T. G. Kwon, M. Eto et al., "Axitinib versus placebo as an adjuvant treatment of renal cell carcinoma: results from the phase III, randomized ATLAS trial," *Annals of Oncology*, vol. 29, no. 12, pp. 2371–2378, 2018.
- [25] E. Galligioni, M. Quaia, A. Merlo et al., "Adjuvant immunotherapy treatment of renal carcinoma patients with autologous tumor cells and bacillus Calmette-Guèrin: Five-year results of a prospective randomized study," *Cancer*, vol. 77, pp. 2560–2566, 1996.
- [26] D. Jocham, A. Richter, L. Hoffmann et al., "Adjuvant autologous renal tumour cell vaccine and risk of tumour progression in patients with renal-cell carcinoma after radical nephrectomy: phase III, randomised controlled trial," *The Lancet*, vol. 363, no. 9409, pp. 594–599, 2004.
- [27] C. Wood, P. Srivastava, R. Bukowski et al., "An adjuvant autologous therapeutic vaccine (HSPPC-96; vitespen) versus observation alone for patients at high risk of recurrence after nephrectomy for renal cell carcinoma: a multicentre, open-label, randomised phase III trial," *The Lancet*, vol. 372, no. 9633, pp. 145–154, 2008.
- [28] C. Lebacle, K. Bensalah, J. Bernhard et al., "Evaluation of axitinib to downstage cT2a renal tumours and allow partial nephrectomy: a phase II study," *BJU International*, 2018.
- [29] K. Tzogani, V. Skibeli, I. Westgaard et al., "The European medicines agency approval of axitinib (Inlyta) for the treatment of advanced renal cell carcinoma after failure of prior treatment with sunitinib or a cytokine: summary of the scientific assessment of the committee for medicinal products for human use," *The Oncologist*, vol. 20, no. 2, pp. 196–201, 2015.
- [30] Merck Sharp Dohme Corp, "A phase III, randomized, double-blind, placebo-controlled clinical trial of pembrolizumab (MK-3475) as monotherapy in the adjuvant treatment of renal cell carcinoma post nephrectomy (KEYNOTE-564)," National Library of Medicine (US), Bethesda, Md, USA, 2000, <https://clinicaltrials.gov/ct2/show/NCT03142334>.
- [31] Pfizer Inc., "A study of avelumab with axitinib versus sunitinib in advanced renal cell cancer (JAVELIN Renal 101)," National Library of Medicine (US), Bethesda, MD, USA, 2000, <https://clinicaltrials.gov/>.
- [32] Merck Sharp Dohme Corp, "A study evaluating the effect of pembrolizumab (MK-3475) in participants with renal cell cancer (MK-3475-031)," National Library of Medicine (US), Bethesda, Md, USA, 2000, <https://clinicaltrials.gov/ct2/show/NCT02212730>.
- [33] M. Allaf, "Study of neoadjuvant nivolumab in patients with non-metastatic stage II-IV clear cell renal cell carcinoma," National Library of Medicine (US), Bethesda, Md, USA, 2000, <https://clinicaltrials.gov/ct2/show/NCT02575222NLM>.
- [34] H. Lee, J. Jimenez, S. Wang et al., "PD35-12 neoadjuvant sunitinib is associated with improved oncologic outcomes for patients with tumor thrombus in renal cell carcinoma: a multicenter analysis," *The Journal of Urology*, vol. 193, article e764, 2015.
- [35] Y. Zhang, Y. Li, J. Deng et al., "Sorafenib neoadjuvant therapy in the treatment of high risk renal cell carcinoma," *Plos One*, vol. 10, Article ID e0115896, 2015.
- [36] N. B. Haas, J. Manola, R. G. Uzzo et al., "Adjuvant sunitinib or sorafenib for high-risk, non-metastatic renal-cell carcinoma (ECOG-ACRIN E2805): A double-blind, placebo-controlled, randomised, phase 3 trial," *The Lancet*, vol. 387, no. 10032, pp. 2008–2016, 2016.
- [37] R. J. Motzer, N. B. Haas, F. Donskov et al., "Randomized phase III trial of adjuvant pazopanib versus placebo after nephrectomy in patients with localized or locally advanced renal cell carcinoma," *Journal of Clinical Oncology*, vol. 35, no. 35, pp. 3916–3923, 2017.
- [38] R. J. Motzer, A. Ravaud, J. Patard et al., "Adjuvant sunitinib for high-risk renal cell carcinoma after nephrectomy: subgroup analyses and updated overall survival results," *Eur Urol* 73:6268, vol. 73, pp. 62–68, 2018.
- [39] R. J. Motzer, E. Jonasch, N. Agarwal et al., "Version 2.2017: clinical practice guidelines in oncology," *Journal of the National Comprehensive Cancer Network*, vol. 15, Article ID 804834, pp. 804–834, 2017.
- [40] Hoffmann-LaRoche, *A phase III, multicenter, randomized, placebo-controlled, double-blind study of atezolizumab (Anti-PD-L1 Antibody) as adjuvant therapy in patients with renal cell carcinoma at high risk of developing metastasis following nephrectomy*, National Library of Medicine (US), Bethesda, MD, USA, 2000.
- [41] J. Larkin, *An international investigator-led phase III multi arm multi stage multi-centre randomized controlled platform trial of adjuvant therapy in patients with resected primary renal cell carcinoma (RCC) at high or intermediate risk of relapse*, National Library of Medicine, Bethesda, Md, USA, 2000, <https://clinicaltrials.gov/>.
- [42] K. Chamie, N. M. Donin, P. Klöpfer et al., "Adjuvant weekly girentuximab following nephrectomy for high-risk renal cell carcinoma," *JAMA Oncology*, 2017.
- [43] A. A. van der Veldt, M. R. Meijerink, A. J. van den Eertwegh et al., "Sunitinib for Treatment of Advanced Renal Cell Cancer: Primary Tumor Response," *Clinical Cancer Research*, vol. 14, no. 8, pp. 2431–2436, 2008.
- [44] A. A. Thomas, B. I. Rini, B. R. Lane et al., "Response of the primary tumor to neoadjuvant sunitinib in patients with advanced renal cell carcinoma," *The Journal of Urology*, vol. 181, no. 2, pp. 518–523, 2009.
- [45] A. Bex, P. Mulders, M. Jewett et al., "Comparison of immediate vs deferred cytoreductive nephrectomy in patients with synchronous metastatic renal cell carcinoma receiving sunitinib," *JAMA Oncology*, vol. 5, pp. 164–170, 2019.
- [46] A. Mejean, A. Ravaud, and S. Thezenas, "Sunitinib alone or after nephrectomy in metastatic renal-cell carcinoma," *European Urology*, vol. 74, pp. 842–843, 2018.
- [47] N. J. Hellenthal, W. Underwood, R. Penetrante et al., "Prospective clinical trial of preoperative sunitinib in patients with renal cell carcinoma," *The Journal of Urology*, vol. 184, no. 3, pp. 859–864, 2010.
- [48] C. L. Cowey, C. Amin, R. S. Pruthi et al., "Neoadjuvant clinical trial with sorafenib for patients with stage II or higher renal cell carcinoma," *Journal of Clinical Oncology*, vol. 28, no. 9, pp. 1502–1507, 2010.
- [49] B. I. Rini, J. Garcia, P. Elson et al., "The Effect of Sunitinib on Primary Renal Cell Carcinoma and Facilitation of Subsequent Surgery," *The Journal of Urology*, vol. 187, no. 5, pp. 1548–1554, 2012.
- [50] J. A. Karam, C. E. Devine, D. L. Urbauer et al., "Phase 2 trial of neoadjuvant axitinib in patients with locally advanced non-metastatic clear cell renal cell carcinoma," *European Urology*, vol. 66, no. 5, pp. 874–880, 2014.
- [51] M. L. McDonald, B. R. Lane, J. Jimenez et al., "Renal Functional Outcome of Partial Nephrectomy for Complex R.E.N.A.L. Score

- Tumors With or Without Neoadjuvant Sunitinib: A Multicenter Analysis,” *Clinical Genitourinary Cancer*, vol. 16, no. 2, pp. e289–e295, 2018.
- [52] J. L. Silberstein, F. Millard, R. Mehrazin et al., “Feasibility and efficacy of neoadjuvant sunitinib before nephron-sparing surgery,” *BJU International*, vol. 106, no. 9, pp. 1270–1276, 2010.
- [53] B. I. Rini, E. R. Plimack, T. Takagi et al., “A Phase II Study of Pazopanib in Patients with Localized Renal Cell Carcinoma to Optimize Preservation of Renal Parenchyma,” *The Journal of Urology*, vol. 194, no. 2, pp. 297–303, 2015.
- [54] B. R. Lane, I. H. Derweesh, H. L. Kim et al., “Presurgical sunitinib reduces tumor size and may facilitate partial nephrectomy in patients with renal cell carcinoma,” *Urologic Oncology: Seminars and Original Investigations*, vol. 33, no. 3, pp. 112.e15–112.e21, 2015.
- [55] N. G. Cost, S. E. Delacroix Jr., J. P. Sleeper et al., “The impact of targeted molecular therapies on the level of renal cell carcinoma vena caval tumor thrombus,” *European Urology*, vol. 59, no. 6, pp. 912–918, 2011.
- [56] P. Bigot, T. Fardoun, J. C. Bernhard et al., “Neoadjuvant targeted molecular therapies in patients undergoing nephrectomy and inferior vena cava thrombectomy: is it useful?” *World Journal of Urology*, vol. 32, no. 1, pp. 109–114, 2014.
- [57] M. Voss, “Nivolumab in treating patients with high-risk non-metastatic kidney cancer,” National Library of Medicine (US), Bethesda, Md, USA, 2000, <https://clinicaltrials.gov/ct2/show/NCT02595918>.
- [58] A. Harshman, “A phase 3 randomized study comparing Peri-operative Nivolumab vs. observation in patients with localized renal cell carcinoma undergoing nephrectomy (PROSPER RCC),” in *ECOG-ACRIN Cancer Research Group*, National Library of Medicine (US), Bethesda, Md, USA, 2000, <https://clinicaltrials.gov/ct2/show/NCT03055013>.
- [59] B. Rini, “A Phase Ib trial of neoadjuvant durvalumab (MEDI4736) +/- Tremelimumab in locally advanced renal cell carcinoma,” National Library of Medicine (US), Bethesda, Md, USA, 2000, <https://clinicaltrials.gov/>.
- [60] T. Schwaab, in *Vaccine therapy before surgery in treating patients with localized kidney cancer*, National Library of Medicine (US), Bethesda, Md, USA, 2000, <https://clinicaltrials.gov/>.
- [61] I. H. Derweesh, “Prior axitinib as a determinant of outcome of renal surgery (PADRES),” National Library of Medicine (US), Bethesda, Md, USA, 2000, <https://clinicaltrials.gov/>.
- [62] R. P. Kopp, R. Mehrazin, K. L. Palazzi et al., “Survival outcomes after radical and partial nephrectomy for clinical T2 renal tumours categorised by R.E.N.A.L. nephrometry score,” *BJU International*, vol. 114, no. 5, pp. 708–718, 2014.
- [63] R. P. Kopp, M. A. Liss, and R. Mehrazin, “Analysis of renal functional outcomes after radical or partial nephrectomy for renal masses  $\geq 7$  cm using the RENAL score,” *Urology*, vol. 86, Article ID 312320, pp. 312–320, 2015.
- [64] R. Bertolo, R. Autorino, and G. Simone, “Outcomes of robot-assisted partial nephrectomy for clinical T2 renal tumors: a multicenter analysis (ROSULA Collaborative Group),” *European Urology*, vol. 74, Article ID 226232, pp. 226–323, 2018.
- [65] C. A. Field, B. H. Cotta, J. Jimenez et al., “Neoadjuvant sunitinib decreases inferior vena caval thrombus size and is associated with improved oncologic outcomes: a multicenter comparative analysis,” *Clinical Genitourinary Cancer*, 2019.



**Hindawi**

Submit your manuscripts at  
[www.hindawi.com](http://www.hindawi.com)

