# Best Practices for the Management of Treatment-Related Adverse Events in Renal Cell Carcinoma

## Introduction

The combination of immunotherapy and tyrosine kinase inhibitors (TKIs) in the treatment of renal cell carcinoma has significantly improved outcomes and changed the treatment landscape of the disease in recent years. However, combination therapy can present an array of challenges for providers, from clinical hurdles to logistical barriers. To optimize therapy in patients, clinicians must understand and overcome barriers to treatment, including toxicity management, financial burdens, and care coordination issues.

In part with its education program, *Best Practices for the Management of Treatment-Related Adverse Events in Renal Cell Carcinoma*, in partnership with the Advanced Practitioner Society for Hematology and Oncology (APSHO), the Kidney Cancer Association, and with support by Pfizer, the Association of Community Cancer Centers (ACCC) conducted a provider survey in 2021 to garner insights on current practice patterns related to care for patients with renal cell carcinoma. The survey explored treatment selection, management of immune-related adverse events (irAEs), care coordination, patient education, prior authorization, and barriers to optimal management of patients with renal cell carcinoma. Results from this survey were analyzed and ACCC shares this report on the current state of care for patients with renal cell carcinoma.

## Current Snapshot

In 2023, it is estimated that 81,800 adults will be diagnosed with renal cell carcinoma, accounting for approximately 4% of all new cancer cases in the United States.[1] Renal cell carcinoma occurs primarily in individuals aged 60 to 80 years and impacts men twice as much as women. About 80% of cases are diagnosed at early stages and approximately 77% of patients survive at least 5 years. Five-year survival for metastatic disease, however, is dismal at only 15%.[1]

Early stages of renal cell carcinoma are predominantly managed with surgical resection in the form of partial or radical nephrectomy, often followed by adjuvant systemic therapy to prolong relapse-free survival. The treatment of metastatic disease, on the other hand, focuses on systemic therapy. In the past few decades, discoveries regarding the immunogenic and angiogenic nature of renal cell carcinoma have fueled the development of increasingly effective targeted therapy and immunotherapy regimens.

Since 2005, 7 different TKIs have been approved for use in renal cell carcinoma, including sorafenib (Nexavar), sunitinib (Sutent), pazopanib (Votrient), axitinib (Inlyta), cabozantinib (Cabometyx), lenvatinib (Lenvima), and tivozanib (Fotivda).[2] These TKIs work on a variety of signal transduction targets, with the primary target in renal cell carcinoma being vascular endothelial growth factor receptor (VEGFR). By inhibiting the VEGF pathway, TKIs prevent tumor angiogenesis, which is essential to the development and survival of renal cell carcinoma.[3]

Another pathway critical to disease progression amenable to treatment targeting is the immune checkpoint pathway. Blockade of the immune checkpoints CTLA-4 or PD-1 activates the immune system to fight against the tumor. Targeting both of these pathways simultaneously has been shown to produce a synergistic effect against the tumor, leading to better outcomes.[3] Thus, the gold standard treatment for renal cell carcinoma has evolved in recent years from TKI monotherapy to a combination of immune checkpoint inhibitors (ICI) with antiangiogenic TKIs.

In 2019, the landmark KEYNOTE-426 (NCT02853331) trial showed that pembrolizumab (Keytruda) plus axitinib (Inlyta) significantly prolonged progression-free survival and overall survival, and enhanced response rates in

the frontline setting compared with single-agent sunitinib (Sutent).[4] In the same year, avelumab (Bavencio) plus axitinib (Inlyta) was also found to improve progression-free survival over sunitinib (Sutent).[5] More recently, nivolumab (Opdivo) plus cabozantinib (Cabometyx) and pembrolizumab (Keytruda) plus lenvatinib (Lenvima) have also demonstrated superiority to TKI monotherapy.[6,7]

## ACCC Survey Outcomes

In a survey of 104 providers, ACCC garnered insights into the practice patterns related to the care journey of patients with renal cell carcinoma. Respondents represented many roles across the multidisciplinary care team, including oncology nurses (27%), nurse practitioners (12%), clinical nurse specialists (10%), pharmacists (8%), physician assistants (6%), and others (37%). Forty-three percent of participants worked in community cancer programs and 38% reported treating 1 to 25 patients with renal cell carcinoma per year.

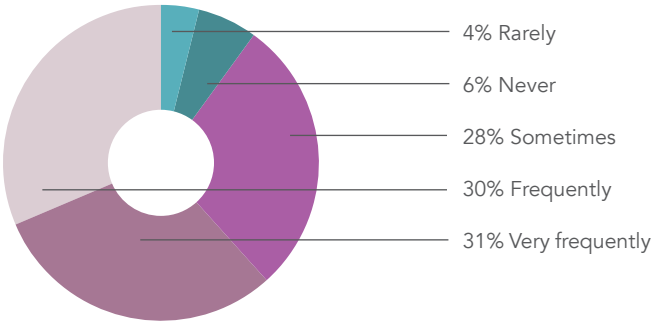
In the survey, almost half of providers routinely used pembrolizumab (Keytruda) plus axitinib (Inlyta) as initial treatment, followed by nivolumab (Opdivo) plus cabozantinib (Cabometyx), avelumab (Bavencio) plus axitinib (Inlyta), and pembrolizumab (Keytruda) plus lenvatinib (Lenvima).

The ACCC survey showed that the typical time frame from treatment decision to initiation of ICI and TKI therapy is 6 to 10 days for nearly half of all practices. Moreover, one-quarter of respondents indicated that 11 to 20 days is their usual time frame. Treatment delays of regimens with oral oncolytics often occur due to the numerous steps involved in processing these medications. Forty-six percent of sites reported "occasional" TKI delays leading to initiation of treatment with pembrolizumab alone and 15% of sites noted that these delays occur "often," highlighting a critical area of opportunity.

## Risk Scoring

When treating a patient with newly diagnosed advanced renal cell carcinoma, survey results indicated that most providers frequently or very frequently use a risk score to determine treatment options; however, more than one-third do not conduct risk scoring on a regular basis **(Figure 1).**

**Figure 1.** Utilization of Risk Scores During Treatment Planning




Risk scoring is an important component in the diagnosis of renal cell carcinoma to help gauge survival and direct treatment based on a patients' prognostic factors. The 2 main risk stratification algorithms currently used are the International Metastatic Renal Cell Carcinoma Database Consortium (IMDC) and Memorial Sloan Kettering Cancer Center (MSKCC) criteria.[2] Both of these tools evaluate several prognostic factors, including performance status, time of diagnosis to treatment, serum calcium, and hemoglobin. Based on the number of poor prognostic indicators, a patient may be stratified as favorable/low-, intermediate-, or poor-risk disease. Combination ICI and TKI is indicated in all risk levels, whereas ipilimumab plus nivolumab is preferred in patients with intermediate- or poor-risk disease.[2]

## Practice Patterns for Combination Immunotherapy and TKI Regimens

Although combination immunotherapy and TKI regimens have drastically improved outcomes, they are not without drawbacks. At least 75% of patients receiving combination ICI plus TKI experienced grade 3 or higher toxicities in clinical studies, most notably hypertension, diarrhea, and liver enzyme abnormalities. Many of the adverse events (AEs) associated with TKIs stem from their inhibition of the VEGF pathway; hypertension, impaired wound healing, proteinuria, hemorrhage, and gastrointestinal perforation are all potential sequela of blocking angiogenesis.[8] ICIs can cause irAEs in virtually any organ at any time. Depending on the severity of the irAE, the ICI is typically held, and systemic steroids can be started for treatment.[9]

TKIs can also be held in the setting of toxicities, but unlike ICIs, their doses may be modified for better tolerability. According to the ACCC survey, there are varied practices

in how cancer centers proceed with implementing a TKI dose reduction. Many practice sites rely on pharmacists or advanced practice providers (APPs) to assess the need for dose reduction, and a final decision is made in conjunction with the oncologist. Some sites noted that their pharmacists can modify the dose based on collaborative practice agreements, whereas one site reported that only physicians could adjust orders at their center.

Overall, use of combination therapy warrants frequent monitoring and extensive education to patients and caregivers. In the ACCC survey, 38% of respondents noted that patients were most likely to be monitored for adverse events from axitinib on day 1 of each cycle, whereas 28% reported weekly monitoring. With pembrolizumab-related toxicities, most providers are monitoring on day 1 of every cycle in addition to telephone/office visits midcycle.

## Patient Education

Patient education, a critical component of ICI and TKI therapy, was another key area explored through the ACCC survey. Although approximately a quarter of respondents reported that patient education is conducted by oncologists, other members of the care team, such as infusion nurses, clinic nurses, APPs, and pharmacists, can also be responsible for this role **(Figure 2)**. Separate office visits account for nearly half of education sessions (46%); however, sessions may also take place on the first day of treatment (37%) or via telephone visits (15%). Once patients begin their TKI regimens, monitoring for adherence and triaging of AEs is also conducted by the care team **(Figure 3)**.

**Figure 2.** Responsibility for Patient Education

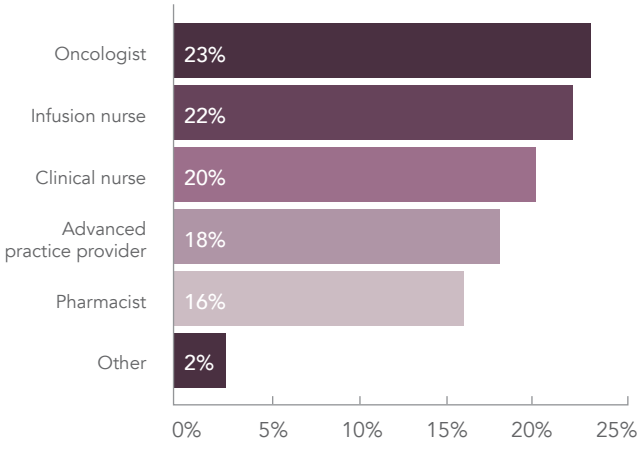
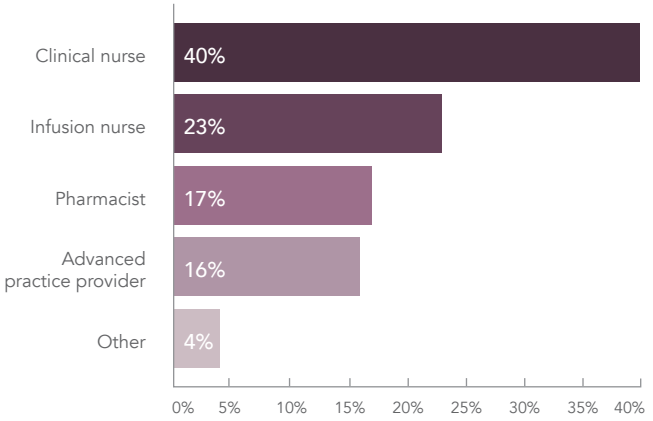



**Figure 3.** Responsibility for Adherence Montoring and Adverse Events Triage

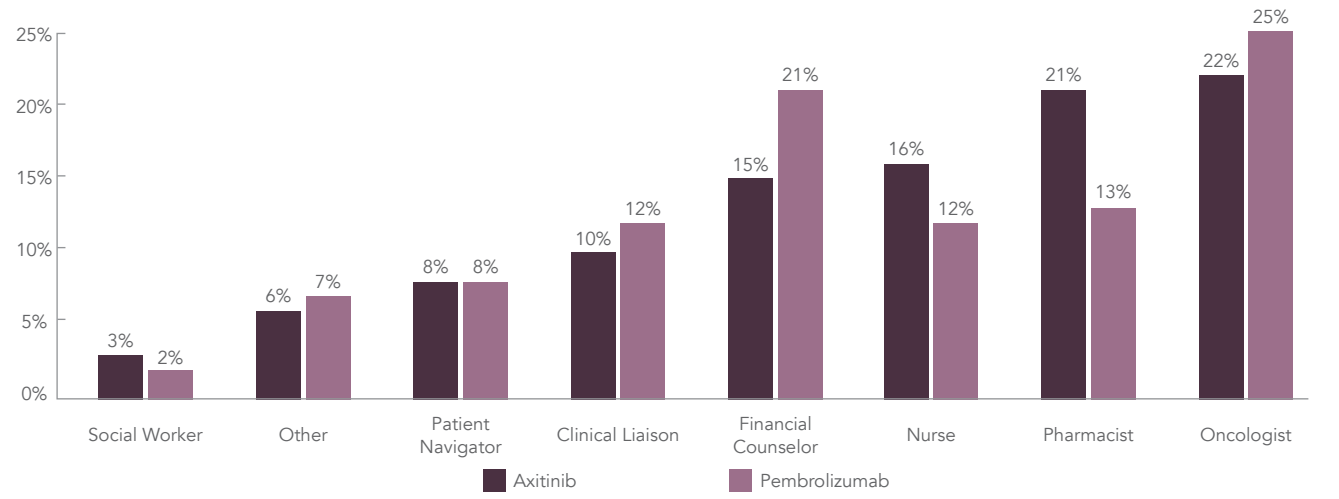



## Considerations for Oral Oncolytics

The dispensing and authorization for oral oncolytics was another key area examined in the ACCC survey. According to survey results, depending on the patients' insurance, oral oncolytics may be filled at various locations; some may have a significantly longer turnaround time for the patient to receive the medication than others. Both health-system specialty pharmacies and external mail-order specialty pharmacies fill TKI prescriptions as indicated by approximately one-third of respondents. Other sites that fill TKIs include medically integrated dispensing pharmacies (14%), local retail pharmacies (12%), and manufacturers for free drugs (9%).

When a prior authorization is required for TKI and ICI regimens, the survey found that oncologists and pharmacists provide roughly 40% of all TKI authorizations and oncologists and financial counselors provide nearly 50% of ICI authorizations. However, authorizations may also be provided by other members of the care team, such as nurses, financial counselors, patient navigators, and others (eg, pharmacy liaisons, social workers, or billing specialists). Financial counselors are also primarily responsible (54%) for providing out-of-pocket estimates to patients, though this responsibility is also shared across the care team **(Figure 4).**

**Figure 4.** Who Completes Prior Authorizations?




## Conclusion

The treatment landscape of renal cell carcinoma has expanded substantially in the past few decades to include a plethora of TKI and ICI therapy options. Combination ICI and TKI regimens are now the standard of care in the first-line treatment of metastatic disease. Although these regimens have significantly enhanced outcomes for patients, they come at a cost of severe toxicities and logistical hurdles. The ACCC survey has identified real-world practice patterns related to the management and monitoring of patients prescribed with ICI and TKI combinations. Opportunities exist to increase utilization of risk assessments, create patient education materials for the multidisciplinary cancer care team, and address the optimal frequency of AE monitoring. From this important work, ACCC is better positioned to implement programs that will help overcome barriers to optimal care in patients with renal cell carcinoma.

For more information and resources, visit the ACCC program webpage **Best Practices for the Management of Treatment-Related Adverse Events in Renal Cell Carcinoma**

ACCC
Association of Community Cancer Centers

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APSHO Advanced Practitioner Society for Hematology and Oncology

KidneyCancerAssociation®

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