

# 2022 WUOF/SIU International Consultation on Urological Diseases: Management of Toxicity and Side Effects of Systemic Therapy for Renal Cell Carcinoma

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## Abstract

Standard approved systemic treatment options for the management of renal cancer have entirely transformed in the last 15 years and now comprise molecularly targeted therapies against the vascular endothelial growth factor receptor (VEGFR) and the mammalian target of rapamycin (mTOR) as well as immune checkpoint inhibitors. These agents may be used alone as monotherapies but increasingly are used in various combinations. The associated important improvements in cancer control and survival have therefore been accompanied by a range of new toxicities. Good management of these toxicities is important for patient safety and quality of life, and also to optimize patients' opportunity to continue with and therefore benefit from these therapies. The most common toxicities associated with VEGFR tyrosine kinase inhibitors are fatigue, skin rashes, gastrointestinal, stomatitis, hypertension and other cardiovascular toxicities, and hematological and endocrine dysfunction. Common side effects of mTOR inhibitors include asthenia, stomatitis, skin rashes, pneumonitis, metabolic changes and infections. Checkpoint inhibitors can lead to toxicities of any organ system with those seen most frequently including dermatologic, gastrointestinal and hepatic, endocrine, musculoskeletal, and pulmonary, whilst renal, hematological, ophthalmic, cardiac and neurological toxicities are seen less often. In general terms, toxicity management should start preemptively with patient education and may also include a combination of supportive approaches, dose reduction, schedule alteration, treatment interruption and occasionally treatment cessation. Treatment of individual toxicities is dependent on the likely causative agent and is guided by its grade or severity. Specific recommendations for management are discussed in this chapter.

## Introduction

Since the mid-2000s, the introduction of new systemic therapies has transformed the management of renal cell carcinoma (RCC). Vascular endothelial growth factor receptor (VEGFR) tyrosine kinase inhibitors (TKIs), mammalian target of rapamycin (mTOR) inhibitors (mTORIs), and most recently immune checkpoint inhibitors (CPIs) have led to dramatically improved outcomes in advanced disease. In the past 5 years, several studies have demonstrated improved survival for the combination of CPIs and TKIs or the combination of the 2 CPI agents nivolumab and ipilimumab compared to first-line therapy with single-agent TKIs, and these combinations are now established as standard of care[1–4]. The CPI pembrolizumab is also now approved as adjuvant therapy following

### Key Words

Renal cell carcinoma, treatment-related adverse events, vascular endothelial growth factor receptor tyrosine kinase inhibitors, mTOR inhibitors, immune checkpoint inhibitors

### Competing Interests

None declared.

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## Abbreviations

CPI	immune checkpoint inhibitor
CTCAE	Common Terminology Criteria for Adverse Event
CTLA-4	cytotoxic T-lymphocyte antigen 4
irAE	immune-related adverse event
mRCC	metastatic renal cell carcinoma
mTOR	mammalian target of rapamycin
mTORI	mammalian target of rapamycin inhibitor
PD-1	programmed cell death 1 receptor
RCC	renal cell carcinoma
TRAE	treatment-related adverse event
VEGFR	vascular endothelial growth factor receptor

resection of high-risk localized disease, or following nephrectomy and full resection of all metastatic lesions[5]. However, alongside their beneficial effects, these agents can cause a range of toxicities. Optimal management of such side effects is required to ensure safe treatment, manageable quality of life, and optimal drug delivery.

## General Principles of RCC Toxicity Management

Prior to initiating systemic therapy for RCC, the patient's current fitness, medical history and comorbidities, and concurrent medications should be considered. This allows for identification of patients at greater risk for toxicity and can trigger targeted pretreatment investigations, such as evaluation of cardiac, endocrine, gastrointestinal, or respiratory status. It may also highlight use of cytochrome P450 3A4 (CYP3A4) enzyme inducers or inhibitors that will interact with the planned RCC treatment[6].

When toxicities arise, they should be graded according to the Common Terminology Criteria for Adverse Events (CTCAE)[7] in conjunction with guidelines for immune-related adverse events (irAEs) to help select optimal management strategies. These include treatment interruption, dose or schedule modification, or occasionally treatment cessation, each of which has a role to play according to the severity or "grade" of the toxicity. Early recognition and intervention aids optimal management of treatment-related adverse events (TRAEs). Support and education for patients, general physicians, and oncologists therefore minimizes the risks associated with these treatments. This is particularly important in the first few months after treatment initiation, but ongoing vigilance is required throughout, especially for CPI-induced toxicities, which can emerge late into, or even after, treatment.

## Toxicity of VEGFR TKIs

VEGFR TKIs including axitinib, cabozantinib, lenvatinib, pazopanib, sorafenib, sunitinib, and tivozanib are highly effective treatments for advanced RCC, with approvals by the United States Food and Drug Administration (FDA) both as single agents and in combination with CPIs or mTOR inhibitors. Collectively, these agents have led to a marked improvement in survival compared with the "pre-TKI" era[8–14]. VEGFR TKIs have varying potency and selectivity for VEGFRs and other tyrosine kinase receptors including platelet-derived growth factor receptor (PDGF), MET, and c-KIT, which contributes to differences in their toxicity and clinical profiles. Most patients experience some side effects, with TRAE rates for all-grade toxicity > 98% in the registration clinical trials and grade  $\geq 3$  toxicity in 10% to 15% of patients. Dose interruptions were reported in 19% to 40% of patients, dose reductions in 14% to 46%, and treatment discontinuation in 4% to 21%. The most common TRAEs reported in registration trials are skin, gastrointestinal, stomatitis, hypertension, hematological abnormalities, fatigue, and endocrine dysfunction (Table 1).

## Management of VEGFR TKI–Associated Toxicities

General principles of managing VEGFR TKI–induced toxicities involve supportive interventions, treatment interruption, dose reduction and, particularly with sunitinib, schedule modification, with occasional treatment discontinuation. Grade 1 and 2 toxicities can often be managed with supportive approaches in the first instance but may benefit from temporary treatment interruption. For treatment-related toxicities grade  $\geq 3$ , treatment interruption is usually required, other than for some laboratory abnormalities. Subsequent dose reduction or schedule modification may be needed.

Most VEGFR TKIs are administered on a continuous dosing schedule. Sunitinib, however, is routinely administered on a dosing schedule that incorporates treatment-free periods: its approved starting dose and schedule is 50 mg daily for 4 weeks followed by a 2-week treatment break (4/2). Several nonrandomized studies[15–17] and the prospective SURF study[18] have shown that the alternate schedule of 2 weeks continuous dosing followed by a 1-week treatment break (2/1) reduces toxicity with no apparent compromise to efficacy. This schedule is not recommended at initiation of sunitinib but can be a useful switch option for therapy management. In selected cases in clinical practice, similar dosing regimens or "drug holidays" can be used for the management of toxicity associated with other VEGFR TKIs[19,20].

Recognized guidelines for VEGFR TKI–driven toxicities should be followed where available. However, unlike

**TABLE 1.**

Safety outcomes reported in pivotal clinical trials of vascular endothelial growth factor receptor tyrosine kinase inhibitors in metastatic renal cell carcinoma

	<b>Sunitinib</b> first line NCT00083889 n = 375 17215529[13]		<b>Pazopanib</b> first or second line, NCT00334282 n = 290 20100962[11]		<b>Tivozanib</b> first or second line NCT01030783 n = 260 24019545[12]		<b>Cabozantinib</b> first line NCT01835158 n = 78 28199818[10]		<b>Axitinib</b> first line NCT00835978 n = 192 NCT00920816[19]		<b>Lenvatinib</b> second line NCT01136733 n = 52 26482279[9]	
<b>TRAE leading to discontinuation in %</b>	8		NR		4		21		4			
<b>Death due to TRAE — n (%)</b>	NR		4 (1)		NR		3 (4)		None			
<b>Adverse event in %</b>	All	Grade 3/4	All	Grade 3/4	All	Grade 3/4	All	Grade 3/4	All	Grade 3/4	All	Grade 3/4
Diarrhea	53	5	52	4	23	2	72	10	50	9	71	12
Fatigue	51	7	19	2	19	5	86	6	33	5	50	8
Nausea	44	3	26	<1	12	<1	32	3	20	1	62	8
Stomatitis	25	1	—	—	11	<1	36	5	—	—	25	2
Hypertension	24	8	40	4	44	27	81	28	49	13	48	17
Vomiting	24	4	21	2	—	—	—	—	—	—	38	4
Hand-foot syndrome	20	5	—	—	14	2	42	8	26	7	15	0
Anorexia	—	—	22	2	18	3	47	5	—	—	48	6
Back pain	—	—	—	—	14	3	—	—	—	—	21	0
Decreased appetite	—	—	—	—	10	<1	—	—	29	2	58	4
Lower respiratory tract infection	—	—	—	—	—	—	—	—	—	—	8	8
<b>Laboratory abnormality</b>												
Neutropenia	72	11	34	1	11	2	15	0	—	—	—	—
Thrombocytopenia	65	8	32	1	18	<1	40	1	—	—	—	—
Lymphopenia	60	12	31	4	—	—	—	—	—	—	—	—
Leukopenia	60	5	0	0	—	—	12	0	—	—	—	—
AST increase	52	2	53	8	37	2	62	3	—	—	—	—
Increased lipase	52	13	—	—	46	11	—	—	—	—	—	—
ALT increase	46	3	53	12	28	1	55	5	—	—	—	—
Hyponatremia	—	—	31	5	—	—	—	—	—	—	—	—
Proteinuria	3	—	—	—	72	3	—	—	—	—	31	19
Hypothyroidism	—	—	—	—	—	—	—	—	—	—	37	2

All adverse events grade 3 or worse that occurred in at least 5% of patients in one of the trials are reported.

ALT: alanine transaminase; AST: aspartate transaminase; NR: not reported in cited publication; TRAE: treatment-related adverse event.

for toxicities associated with immune CPIs, there are no regularly updated consensus guidelines, and recommendations are primarily derived from clinical expertise. Practical recommendations for common VEGFR TKI-associated toxicities are summarized in [Table 2](#). A related and important point concerns hypertension as a potential biomarker for efficacy, best demonstrated with axitinib. It has been shown that blood pressure rise is somewhat correlated with axitinib serum concentration and that correct axitinib dose titration, including

dose increase according to its approval, is associated with improved response to treatment[19].

### Toxicity of mTOR Inhibitors

The mTORIs temsirolimus and everolimus are usually well tolerated, with low rates of grade 3 and 4 adverse events[21–24]. Common side effects include asthenia, stomatitis, skin rashes, pulmonary toxicity, metabolic changes particularly hyperglycemia and hyperlipidemia,

**TABLE 2.**

Management recommendations for key toxicities associated with VEGFR tyrosine kinase inhibitors

Toxicity	Management recommendations
Hypertension	Almost all patients commencing these medications experience a dose-dependent elevation in blood pressure. Pretreatment evaluation and treatment of blood pressure and cardiovascular risk essential as treatment-related reduction in LVEF correlates with baseline risk. Blood pressure should be monitored regularly with initiation of antihypertensive therapy $\geq 140/90$ mmHg according to clinical practice guidelines. Nondihydropyridine calcium-channel blockers that inhibit CPY3A4 (verapamil, diltiazem) should be avoided[25].
Fatigue	Fatigue is common and often multifactorial. Monitoring for and treatment of anemia, hypothyroidism, cardiac dysfunction, diarrhea, hypophosphatemia, and low testosterone levels in males can be of help. Dose reduction may be required if fatigue persists despite correcting these factors. Aerobic exercise reduces fatigue in fit patients.
Diarrhea	Dietary adjustment (BRAT diet: bananas rice, applesauce, toast) and increase in fluid intake. Loperamide or pancreatic enzyme supplementation can also be considered in specific cases.
Diarrhea / Emerging data	Probiotics have been shown to reduce the severity of chemotherapy-induced diarrhea; however; have not specifically been evaluated in TKI-induced diarrhea[25]. Fecal microbiota transplantation has recently shown promising results for the treatment of TKI-induced diarrhea[27].
Hand-foot syndrome	Preventative advice includes avoiding unnecessary friction/removing hyperkeratosis prior to treatment and avoiding excessively hot water. For erythema (grade 1), recommend self-care plus moisturizing creams and 20% to 40% urea creams. Pain (grade 2) requires dose interruption/modification with addition of clobetasol 0.05% ointment/topical or systemic analgesia as required[28]. Other dermatologic effects including skin and hair color changes are relatively common, thus patients should be counseled accordingly.
Stomatitis	Stomatitis may result in a significant reduction in food intake and QOL.
Good oral hygiene.	Oral rinses (saline, sodium bicarbonate, or nonalcoholic mouthwash) can be used for mucosal erythema (grade 1). For grade $\geq 2$ mucositis requiring dose interruption/modification; topical anesthetics, mucosal coating agents, and/or benzydamine HCl may be administered as needed for pain[29]
Hypothyroidism	TSH should be measured at baseline and monitored during treatment at least every 3 cycles. Replacement with thyroxine should be considered for patients with TSH above 10 IU/mL[30]

LVEF: left ventricular ejection fraction; QOL: quality of life; TSH: thyroxine stimulating hormone; VEGFR: vascular endothelial growth factor receptor.

and infections[31]. As for VEGFR TKI-related toxicities, the general principles of managing the side effects from mTORIs are to consider treatment interruption, dose reduction, and use of supportive therapies, as well as treatment cessation for grade 3 and 4 toxicities[32]. Key recommendations are summarized in **Table 3**.

### Toxicity of Immune Checkpoint Inhibitors

Immune CPIs are a well-established component of treatment for advanced renal cell carcinoma and now are also approved in the adjuvant setting[2,5,33,34]. While CPIs are well tolerated by many patients, immune checkpoint blockade is associated with a unique collection of irAEs. These irAEs behave differently than the more predictable toxicities oncologists are

accustomed to managing with chemotherapy or targeted therapies, occurring any time between initiation of treatment to many months after treatment cessation.

### Mechanism, Spectrum, and Frequency of CPI-Associated Toxicities

#### Mechanisms of Immune-Related Adverse Events

The exact mechanisms responsible for the development of irAEs are not fully understood. The immune checkpoint proteins cytotoxic T-lymphocyte antigen 4 (CTLA-4) and programmed cell death 1 receptor (PD-1) play important roles in immune homeostasis and self-tolerance, acting to suppress T-cell function. CTLA-4 signaling reduces T-cell proliferation early in the immune response, and PD-1 signaling inhibits activated

**TABLE 3.**  
Management recommendations for key toxicities of mTOR inhibitors

Toxicity	Management recommendations
Stomatitis	One of the most common TRAEs, presenting with an aphthous stomatitis different from cytotoxic induced mucositis[35,36]. Grade 1: Modified diet and alcohol-free mouthwash may alleviate symptoms. Grade ≥ 2: Treatment should be interrupted and can be restarted at full (grade 2) or reduced (grade 3) dose. Grade 4: Treatment should be discontinued permanently in most cases. Investigation to rule out herpes and fungal infection may be helpful[37].
Skin rash	Usually papulopustular/maculopapular, can be pruritic. Avoid heavy sun exposure. Grade 1 (covering < 10% BSA) and grade 2 (covering > 10% to < 30% BSA) toxicity can be managed with topical moisturizers and steroids. Grade 3 toxicity (covering > 30% BSA) may require dose interruption and treatment with low-dose systemic steroids (eg, 10–20 mg prednisolone).
Noninfectious pneumonitis	Characterized by noninfectious, nonmalignant pulmonary inflammatory infiltrates[21,38]. If preexisting pulmonary morbidity, consider baseline LuFT. Grade 1 (radiological findings only): Clinical follow-up sufficient. Grade 2 (cough, SOB, no oxygen requirement): Workup for other causes of symptoms including chest imaging. Grade 3 (interference with ADL or oxygen requirement): Interrupt treatment and start steroids (prednisolone 0.75–1 mg/kg). Treatment can be restarted with a reduced dose. Grade 4 (life-threatening pneumonitis): Start treatment with intravenous steroids (eg, methylprednisolone 2–5 mg/kg). Discontinue treatment permanently. Workup including BAL is recommended.
Endocrine: Hyperglycemia Hyperlipidemia Hypophosphatemia	Common, educate patients regarding symptoms of hyperglycemia, measure and correct according to standard guidelines[39–41]. Grade 2 and 3 hyperglycemia (glucose > 8.9 mmol/L): Treat according to guidelines, focus on avoiding symptomatic hyper- and hypoglycemia.
Infections	Increased risk (candidiasis, pneumonia, invasive fungal infections, and infection reactivation). If high risk, hepatitis and HIV serology and prior TB exposure should be checked and active infection treated.

ADLs: activities of daily living; BAL: bronchoalveolar lavage; BSA: body surface area; LuFT: lung function test; mTOR: mammalian target of rapamycin; SOB: shortness of breath; TRAEs: treatment-related adverse events.

T cells in peripheral tissues[42]. While inhibiting these pathways enables the immune system to recognize and attack the patient's cancer, inflammation of normal tissues through the production of cytokines, autoreactive T cells, and autoantibodies may occur, resulting in irAEs[43,44].

### Range of Immune-Related Adverse Events

The spectrum of irAEs experienced depends on whether the CPI is used in combination or alone and according to the malignancy being treated, alongside yet poorly understood host factors such as an individual's genetics, epigenetics, and microbiome. Overall, dermatological, gastrointestinal, endocrinological, musculoskeletal, and pulmonary irAEs are more common, with renal, hematological, ophthalmological, cardiac, and neurological irAEs seen more rarely[45,46]. IrAEs have a variable and wide range of onset, although typically dermatitis and colitis present early, followed by hepatitis and endocrinopathies, with pneumonitis and nephritis presenting later[47,48]. Fatal irAEs are fortunately rare, with reported rates ranging from 0.36% with anti-PD-1 antibodies to 1.23% in combination with CTLA4[49]. Given the increasing use of CPIs in the treatment of solid cancers in general, and in renal cancer in particular, an absolute increase in irAEs and also the occurrence of rare irAEs are to be expected in these patients[50]. The frequency and severity of irAEs do not appear to be dose-dependent and there is no role for dose reduction following CPI toxicity.

### Immune-Related Adverse Events in RCC

Landmark clinical trials demonstrate that small percentages of patients experience grade 3 or 4 toxicities, with overall benefits for health-related quality of life[51-53] (Table 4). CheckMate 025 investigated nivolumab versus everolimus as second- or subsequent-line treatment in patients with advanced RCC[33], CheckMate 214 investigated the combination of nivolumab and ipilimumab versus sunitinib in the first-line treatment of patients with advanced RCC[2], and KEYNOTE-564 investigated adjuvant pembrolizumab versus placebo following nephrectomy[2]. TRAEs leading to discontinuation of CPI occurred in between 8% to 22% of patients in these trials, as outlined in Table 4.

### Management of CPI-Associated Toxicities

#### General Principles for Management of Immune-Related Adverse Events

The management of irAEs in patients with RCC is the same as in other solid tumors, and detailed guidelines are available from European Society for Medical Oncology (ESMO), American Society of Clinical Oncology (ASCO), Society for Immunotherapy of

Cancer (SITC), and the National Comprehensive Cancer Network (NCCN)[46,54-56]. The guidelines have been developed based on consensus opinion from specialist physicians and oncologists, are regularly updated, and are strongly recommended to guide management of specific toxicities. The overarching principle of management is to control the inflammation that has precipitated the irAE. Management is directed by the severity of the irAE and typically involves prompt immunosuppression with corticosteroids, treatment interruption, with hospitalization and specialist management in more serious cases.

#### Corticosteroids and Corticosteroid-Sparing Agents in Immune-Related Adverse Events

In general, for CTCAE grade 1 irAEs, corticosteroids are not required, and immunotherapy may be continued[46]. For grade 2 irAEs, oral prednisone (or equivalent) may be considered, starting at 0.5–1 mg/kg daily, increasing to 2 mg/kg daily if required. For grade  $\geq 3$  irAEs, oral prednisone at 1–2 mg/kg daily, or equivalent intravenous methylprednisolone, is commenced. Immunotherapy is paused until the irAE has resolved to grade 1 or less and steroids have been weaned, usually over 4 to 6 weeks. In severe or refractory cases, or where steroid sparing is desirable, other immunomodulatory agents may be considered. These agents may have specific immune targets such as TNF $\alpha$  (infliximab), IL-6 (tocilizumab), or  $\alpha 4$  integrin (vedolizumab), or be nonselective, such as mycophenolate mofetil[57]. In such cases, liaising with specialist physicians is of paramount importance.

Restarting immunotherapy treatment may be considered on a case-by-case basis after a grade 3 irAE, but immunotherapy is discontinued after grade 4 irAEs. Most irAEs are reversible with steroid treatment, but endocrinopathies, especially hypothyroidism and diabetes, may require lifelong hormone replacement, although these rarely require steroid treatment[58,59].

#### RCC Outcomes in Patients Who Experience Immune-Related Adverse Events

Although the development of irAEs is not required to benefit from CPI, there are some data, including in RCC, to suggest that patients who experience irAEs have better outcomes, particularly with anti-PD-1 and anti-PD-L1 treatment[60-65]. High-dose steroid treatment is not thought to impact outcomes negatively, although there are conflicting reports in the literature, and patients receiving high-dose corticosteroids at baseline do appear to experience inferior outcomes[43,61]. Immunosuppression with steroids may be associated with side effects including hyperglycemia, weight gain, hypertension, edema, gastritis, anxiety, adrenal insufficiency, osteoporosis, glaucoma, proximal muscle weakness, and opportunistic infections[43]. Supportive

**TABLE 4.**

Safety outcomes reported in pivotal registration clinical trials of immune checkpoint inhibitors in renal cell carcinoma

	<b>Nivolumab</b> mRCC, second or later line, CheckMate 025, NCT01668784 n = 406[33]		<b>Nivolumab &amp; ipilimumab</b> mRCC, first line, CheckMate 214, NCT02231749, n = 547[2,52]		<b>Pembrolizumab</b> adjuvant setting, KEYNOTE-564, NCT03142334 n = 488[5]	
<b>TRAE leading to discontinuation in %</b>	8		22		21	
<b>Death due to TRAE— n (%)</b>	None		8 (1)		2 (<1)	
<b>Toxicity in %</b>	<b>All</b>	<b>Grade 3/4</b>	<b>All</b>	<b>Grade 3/4</b>	<b>All</b>	<b>Grade 3/4</b>
Any	79	19	93	46	79	19
Fatigue	33	2	37	4	30	1
Pruritis	14	0	28	<1	23	<1
Nausea	14	<1	20	1	16	<1
Diarrhea	12	1	27	4	25	2
Reduced appetite	12	<1	14	1	-	-
Rash	10	<1	22	1	20	1
Cough	9	0	—*	—	16	0
Dyspnea	7	1	—	—*	—	—
Pneumonitis	4	1	—	—*	—	—
Hypothyroidism	—	—	16	<1	21	<1
Asthenia	—	—	13	1	10	<1
Vomiting	—	—	11	<1	—	—
Arthralgia	—	—	—	—	22	<1
Headache	—	—	—	—	14	0
Hyperthyroidism	—	—	—	—	12	<1
Increased creatinine	—	—	—	—	10	<1

\*While cough, dyspnea, and pneumonitis were not reported, in the combination arm of the CheckMate 214 study, 1 patient died from pneumonitis, 1 with pneumonia, 1 with immune-mediated bronchitis, and 1 with lung infection.

mRCC: metastatic renal cell carcinoma; NR: not reported in paper; TRAE: treatment-related adverse event.

therapies must therefore be considered for all patients on steroids, including gastric protection, calcium and vitamin D, and pneumocystis pneumonia prophylaxis, particularly for patients requiring a longer course.

### Toxicities of Combination VEGFR TKI/CPI Regimens

Regimens that combine a VEGFR TKI with a CPI have become a standard of care in first-line therapy of advanced RCC due to improved cancer outcomes compared with TKI monotherapy[1,4,66,68]. Collectively, these regimens are regarded as having acceptable safety profiles with manageable toxicity. Given the impressive cancer control conferred by these regimens, patients are often on treatment for many months or years, thus good toxicity management is of great importance for durable good quality of life.

### Spectrum and Frequency of Toxicities with TKI/CPI Combination Regimens

The registration trials of approved TKI/CPI combinations have reported a variety of safety endpoints and toxicities, each compared with sunitinib monotherapy. Although there are differences across both the trial populations and the toxicity measures reported, the data illustrate the acceptable tolerability of each of the regimens in trial populations (Table 5).

The rate of of grade  $\geq 3$  TRAEs reported with the TKI/CPI combinations in registration studies was 57% to 72% (compared with 51% to 59% for the comparator sunitinib in these trials). Across all trials, the most frequently occurring TRAEs were consistently hypertension, raised transaminases, and diarrhea. Discontinuation of at least one of the agents due to TRAEs occurred in 15% to 37% of patients and discontinuation of both in 3% to 13%.

### Management of Toxicities Associated with TKI/CPI Combination Regimens

Optimal management of the toxicities from TKI/CPI combination regimens requires appreciation of the expected range of side effects of each agent. However, there is additional complexity because some toxicities may be caused by both TKIs and CPIs. This requires an approach for identifying the more likely cause.

The common and serious toxicities resulting from VEGFR TKIs and CPIs are described above. Toxicity caused by VEGFR TKIs most commonly manifests in the first few weeks following treatment initiation, whereas toxicities caused by immune CPIs can start acutely or many months into treatment. However, there is considerable variation at the individual patient level, and the toxicity profiles do overlap considerably, therefore despite best efforts, reliable attribution can be challenging. Points to consider include:

1. VEGFR TKIs have considerably shorter half-lives than CPIs. Axitinib has the shortest half-life at 2.5–6 hours, those of lenvatinib and cabozantinib are 28 hours and 100–120 hours, respectively. The half-lives of both pembrolizumab and nivolumab are around 26 days. Thus, VEGFR TKI-driven toxicity, especially from axitinib, typically starts to improve within a few days of treatment interruption, including when used in an axitinib plus CPI combination[69].
2. In some cases, directed investigation may help to differentiate the cause, assess impact and severity, and guide management such as sigmoidoscopy and biopsy for evaluation of colitis; assessment of the pituitary fossa by magnetic resonance imaging (MRI) for hypophysitis; and cardiac MRI to identify immune-mediated myocarditis.

Toxicities should be managed in accordance with the strategies described earlier in this article, including treatment interruption, dose reduction (for TKIs but not CPIs), and treatment discontinuation when indicated. As a general principle, grade 1 and 2 toxicities may not require any intervention other than supportive therapies and monitoring. Grade 3 and higher toxicities usually require at least temporary treatment interruption. When treatment interruption of a TKI/CPI regimen is required and there is uncertainty about the cause, the following pragmatic approach is suggested:

- First stop the TKI. Improvement in toxicity should be seen within a few days if the toxicity is TKI related.
- If there is no improvement after 5 to 7 days, or less for axitinib, interruption of the CPI and initiation of steroids should be considered following a recognized irAE guideline.
- Consider immediate interruption of both agents for severe, clinically significant toxicities.
- Continue to use appropriate supportive measures according to the toxicity.
- Ongoing regular assessment is required until improvement or resolution with vigilance for reemergence during steroid wean or following further treatment.

### Toxicities of Novel Therapeutic Approaches

Ongoing clinical trials are investigating new agents and combinations that will require attention to their tolerability and emergent toxicities. COSMIC-313 (NCT03937219) is a fully recruited, randomized trial assessing the triplet combination of cabozantinib plus ipilimumab and nivolumab in 840 patients with intermediate- and poor-risk advanced RCC[70]. While there should be scrutiny of the tolerability of this triplet regimen, it has been successfully delivered in



a pan-genitourinary phase 1B trial with acceptable tolerability[71].

The hypoxia-inducible factor (HIF)-2 $\alpha$  inhibitor belzutifan was approved by the FDA in 2021 for the treatment of von Hippel-Lindau (VHL)-associated metastatic renal cell carcinoma (mRCC)[72], and its role in sporadic mRCC is being evaluated in a phase 3 trial after promising initial results (NCT04195750)[73]. Belzutifan is relatively well tolerated, although grade  $\geq 3$  AEs were reported in 25% of patients and included grade  $\geq 3$  anemia (related to inhibition of the erythropoietin gene) and hypoxia, thus monitoring for and management of these toxicities is essential[72] including blood transfusion and/or the use of erythropoietin-stimulating agents[74].

### Patient Selection and Toxicity Prediction

Good patient selection is an important tool in ensuring the optimal balance of efficacy with acceptable toxicity and quality of life. The toxicities associated with treatment of RCC are not insignificant, leading to discontinuation of VEGFR TKI therapy in 12% to 24%[75,76], combination nivolumab plus ipilimumab in 22%[2,52], and TKI/CPI combinations in 6% to 11%[1,4,66,68]. Therefore, understanding predictors of toxicity is an important focus of research. Most research in this field to date has evaluated clinical and genomic predictors of toxicity to VEGFR TKI therapy with low body surface area, older age, and female gender identified as possible clinical predictors[77]. Several studies have focused on the role of single-nucleotide polymorphisms (SNPs) in genes related to pharmacodynamic properties of VEGFR TKIs[78–80]. While research has not yet yielded practice-influencing results, it is hoped that large collaborative projects such as the EuroTARGET cohort[81], incorporating analysis of genomic, transcriptomic, and clinical parameters, will produce clinically useful information.

Currently, there are no defined biomarkers that predict toxicity to immune CPIs, although it is apparent that some patients are at greater risk of experiencing irAEs[45,49]. Historically, patients thought to be at higher risk for irAEs have been excluded from clinical trials, so data are lacking, but as real-world experience grows, multidisciplinary strategies for managing such patients are evolving. Patients with chronic viral

infections such as hepatitis and HIV, mild-to-moderate organ dysfunction, autoimmune disease, and even transplant recipients have been successfully treated with CPIs in some circumstances, although a personalized discussion regarding potential risks and benefits is important[60]. There is growing interest in the role of the gut microbiome in modulating both the efficacy and toxicity of CPI therapy. In patients with advanced melanoma who received ipilimumab plus nivolumab, enrichment with *Bacteroides intestinalis* and *Intestinibacter bartlettii* was seen in patients who developed grade  $\geq 3$  adverse events versus those who did not[82]. Investigation of this field continues, including in mRCC.

In the future, as doublet, and potentially triplet, combination regimens are increasingly used, effective strategies to manage toxicity will be needed to transfer clinical trial regimens to more diverse real-world patient populations. Genomic approaches may offer the possibility of refining treatment selection for patients according to expected toxicity profiles. However, at present, there are no robust or validated genomic predictors, therefore selection is reliant on traditional measures of performance status and comorbidities.

### Summary

Toxicity management is an essential component of effective cancer control. In the past 15 years, considerable experience has been gained in the management of the side effects of molecularly targeted therapies, with strategies including dose modification, schedule modification, switching between agents, and use of supportive therapies. Immune checkpoint inhibitors are also now used widely in treatment of mRCC. This advance has necessitated RCC oncologists to develop an understanding of a new range of toxicities and become familiar with new strategies and algorithms that have evolved to manage irAEs, including use of corticosteroids and steroid-sparing agents, as well as increasing involvement of other organ- or system-specific specialists. Combination regimens of CPIs and VEGFR TKIs are now increasingly used, but careful management can balance treatment delivery with tolerable side effects. It is hoped that ongoing research will identify robust means of prospectively identifying those at increased risk for treatment-related toxicities to allow for improved therapy selection at an individual level.

**TABLE 5.**

Safety outcomes reported in pivotal clinical trials for the combinations of tyrosine kinase inhibitors and immune checkpoint inhibitors in first line metastatic renal cell carcinoma and occurred in at least 15% of patients who received the VEGFR TKI / CPI combination

	<b>Axitinib + pembrolizumab</b> First line, KEYNOTE-426, NCT02853331, n = 429[4]		<b>Axitinib + avelumab</b> First line, JAVELIN Renal-101, NCT02684006, n = 442[67]		<b>Cabozantinib + nivolumab</b> First line, CheckMate 9ER, NCT03141177 n = 322[1]		<b>Lenvatinib + pembrolizumab</b> First line, CLEAR, NCT02811861 n = 355[3]	
<b>Treatment discontinuation for TRAE in %</b>								
Both drugs	8		8		3		13	
Either	26		NR		15		37	
<b>Treatment-related deaths— n (%)</b>	4 (< 1)		3 (< 1)		1 (< 1)		4 (1)	
<b>Toxicity in %</b>	<b>All Grades</b>	<b>Grade 3/4</b>	<b>All Grades</b>	<b>Grade 3/4</b>	<b>All Grades</b>	<b>Grade 3/4</b>	<b>All Grades</b>	<b>Grade 3/4</b>
Any	96	63	100	71	100	61	100	82
Diarrhea	54	9	62	7	64	7	61	10
Hypertension	45	22	50	26	35	13	55	30
Fatigue	39	3	42	4	32	3	40	4
Hypothyroidism	35	< 1	25	< 1	34	< 1	47	1
Decreased appetite	30	3	26	2	28	2	40	4
Hand-foot syndrome	28	5	33	6	40	8	29	4
Nausea	29	1	34	1	27	1	36	3
ALT increased	27	13	17	6	28	5	12	4
AST increased	26	7	15	4	25	3	11	3
Dysphonia	25	< 1	31	1	17	< 1	30	0
Cough	21	< 1	23	< 1	17	0	20	0
Constipation	20	0	18	0	12	1	25	1
Arthralgia	18	1	20	1	18	< 1	28	1
Weight decreased	18	3	20	3	11	1	30	8
Proteinuria	18	3	–	–	10	3	30	8
Dyspnea	16	2	20	3	–	–	15	3

Table 5 shows the safety outcomes that were reported in the referenced pivotal trials and occurred in at least 15% of patients who received the VEGFR TKI / CPI combination. ALT: alanine transaminase; AST: aspartate transaminase; CPI: immune checkpoint inhibitor; TRAE: treatment-related adverse event; VEGFR TKI: vascular endothelial growth factor receptor tyrosine kinase inhibitor.

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Safety outcomes reported in pivotal clinical trials for the combinations of tyrosine kinase inhibitors and immune checkpoint inhibitors in first line metastatic renal cell carcinoma and occurred in at least 15% of patients who received the VEGFR TKI / CPI combination

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<b>Toxicity in %</b>	<b>All Grades</b>	<b>Grade 3/4</b>	<b>All Grades</b>	<b>Grade 3/4</b>	<b>All Grades</b>	<b>Grade 3/4</b>	<b>All Grades</b>	<b>Grade 3/4</b>
Stomatitis	16	1	24	2	17	3	35	2
Headache	16	1	21	< 1	16	0	23	1
Vomiting	15	< 1	18	1	17	2	26	3
Asthenia	15	3	15	3	22	< 1	22	5
Pruritis	15	< 1	14	0	19	< 1	17	< 1
Rash	14	< 1	14	1	22	2	27	4
Back pain	13	1	18	1	18	2	17	1
Mucosal inflammation	13	1	14	1	21	1	–	–
Pyrexia	13	0	13	0	12	1	15	1
Abdominal pain	11	1	14	1	16	2	2	2
Dysgeusia	11	< 1	13	0	24	0	12	< 1
Increased lipase	–	–	–	–	17	6	18	13
Hyponatremia	–	–	–	–	16	9	–	–
Increased amylase	–	–	–	–	15	3	18	9

Table 5 shows the safety outcomes that were reported in the referenced pivotal trials and occurred in at least 15% of patients who received the VEGFR TKI / CPI combination. ALT: alanine transaminase; AST: aspartate transaminase; CPI: immune checkpoint inhibitor; TRAE: treatment-related adverse event; VEGFR TKI: vascular endothelial growth factor receptor tyrosine kinase inhibitor.

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