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ORIGINAL ARTICLE

Management of metastatic renal cell carcinoma following prior vascular endothelial growth factor–targeted therapy: A real-world retrospective study from Taiwan

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Abstract

Background: There are limited real-world data to guide the sequencing of targeted therapies in patients with metastatic renal cell carcinoma (mRCC). The objective of this study was to characterize real-world treatment patterns (primarily second line [2L]) after prior vascular endothelial growth factor (VEGF) targeted therapy in an unselected mRCC population from Taiwan between 2013 and 2017. Treatment-related adverse events (TRAEs) and their management were also evaluated (NCT03633579).

Methods: This retrospective cohort study included patients who had received prior VEGF-targeted therapy and were treated at the National Taiwan University Hospital or the Taipei Veterans General Hospital between June 2013 and December 2017. Outcomes were characterized using descriptive statistics.

Results: Overall, 27 patients were included: 22 (81.5%) male; mean standard deviation (SD) age, 63.1 (11.1) years; 18 (66.7%) initiated targeted therapy during the year immediately following mRCC diagnosis. All patients received sunitinib as their first-line (1L) targeted therapy, with a median (range) treatment duration of 10 (1.8–65.8) months. The most common reason for discontinuing 1L sunitinib was disease progression (88.9% of patients). Everolimus was the most common 2L targeted therapy, in 23 patients (85.2%); 4 patients (14.8%) received 2L axitinib. Median (range) duration of 2L therapy was 4.0 (0.1–30.5) months for everolimus and 4.2 (0.5–9.2) months for axitinib. Ten TRAEs were reported among seven patients receiving 2L everolimus: hypertension (n = 5), hand-foot syndrome (n = 2), hyperglycemia (n = 1), renal failure (n = 1), and interstitial pneumonitis (n = 1). The majority (80%) of TRAEs were managed in the outpatient setting. No TRAEs were reported in the axitinib group.

Conclusion: Real-world management of patients with mRCC in Taiwan broadly aligned with clinical guidelines and national reimbursement policy at the time of the study. These findings may be a useful reference for assessing the implications of evolving mRCC management approaches in Taiwan.

Keywords: Metastatic Renal Cell Carcinoma; Real-World; Taiwan; Treatment Patterns; Vascular Endothelial Growth Factor-Targeted Therapy

1. INTRODUCTION

Renal cell carcinoma (RCC) is the most common form of renal cancer worldwide, accounting for an estimated 80% of all renal tumors.[1] Several histological RCC subtypes are recognized, but 75% to 80% of cases are of clear cell histology (ccRCC).[2] The frequently asymptomatic nature of early-stage RCC means that around one-third of patients have metastatic disease (metastatic RCC [mRCC]) at the time of diagnosis.[3,4] Later stage RCC diagnosis is associated with poorer prognosis; the 5-year survival rate for patients with mRCC remains low at approximately 12%.[5]

In recent years, there have been improvements in 5-year overall survival (OS) of patients with RCC, largely driven by advances in treatment strategies rather than in diagnostics.[6] Growing understanding of the underlying molecular pathways involved in RCC pathogenesis and targeted therapeutic approaches have redefined mRCC treatment. Recognition of the association between overexpression of vascular endothelial growth factor (VEGF) and platelet-derived growth factor (PDGF) and progression of RCC,[7–9] for example, has led to the development of multiple therapies targeting the VEGF pathway. A range of targeted therapies are now approved for the management of

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RCC, including VEGF-targeted tyrosine kinase inhibitors (TKIs; eg, sorafenib, sunitinib, pazopanib, axitinib, and cabozantinib), VEGF-targeted monoclonal antibody bevacizumab (in combination with interferon alpha [IFN-α]), and mammalian target of rapamycin (mTOR) inhibitors everolimus and temsirolimus.[7,10] This emergence of new therapeutic agents for RCC has rapidly redefined the treatment landscape and required repeated revision of clinical guidelines and reimbursement policies. Clinical guidance on the management of RCC published by the European Association for Urology (EAU) in 2015, for example, endorsed the use of front-line TKI therapy and its potential to prolong OS and progression-free survival (PFS) when used as a first-line (1L) or second-line (2L) treatment in patients with metastatic ccRCC.[7] Only 5 years later (in 2021[11]), however, updated EAU guidelines[12] recommended combination immune checkpoint inhibitors (CPIs)/TKI therapy as the 1L standard of care.

In Taiwan, clinical practice is guided by international guidelines and also influenced by the national reimbursement policy, set by the National Health Insurance Administration (NHIA).[13] While NHIA policy typically aligns with international guidance, there can be delays in guideline updates being encapsulated within policy revisions. In dynamic treatment landscapes, such as for RCC, this can cause temporary differences between international guidelines and national policy and presents access challenges for clinicians seeking to use new treatment options. During the start of the study (2013–2015), everolimus was the only 2L mRCC treatment approved for reimbursement in Taiwan, with use limited to patients who had failure on prior sorafenib or sunitinib therapy. By the end of the study (2016–2017), axitinib was also approved for reimbursement in Taiwan, limited to use in patients who had failed on prior sunitinib or cytokine therapy.

There are limited data on the routine management of mRCC in Taiwan and limited understanding of the influences of clinical guidelines and reimbursement policy on real-world clinical decision-making. The objective of this study was to characterize real-world treatment patterns and treatment-related adverse events (TRAEs) and their management in an unselected real-world population of patients treated for mRCC after prior VEGF-targeted therapy in Taiwan between 2013 and 2017.

2. METHODS

2.1. Study design and source data

This was a retrospective cohort study using medical records for patients with mRCC treated at the National Taiwan University Hospital (NTUH) or at the Taipei Veterans General Hospital (VGH-TPE) in Taipei, Taiwan (NCT03699579). The study period ran from June 1, 2013, to December 31, 2017, or until the last patient's death or last medical record (if lost to follow-up), whichever occurred first. Patients were identified through medical chart reviews conducted by study nurses, with patient eligibility confirmed by the respective center's lead investigator. As this was a retrospective study, the patients were not required to provide written informed consent. All necessary ethical approvals were secured by the Research Ethics Committees of NTUH and VGH-TPE before the start of the study (IRB numbers 201810108RSC and 2018-11-009AC). The study methods were compliant with local Taiwanese regulations, including Data Protection Laws and Regulations on Human Trials with regard to the processing of personal data and on the free movement of such data.

2.2. Patient population

Eligible patients were aged 20 years or older at the start of the study, had confirmed ccRCC with evidence of metastatic disease (radiological or via computed tomography or magnetic resonance imaging), and initiated subsequent targeted therapy (eg, axitinib, everoliums, and temsirolimus) at one of the study centers. All patients had received at least one prior VEGF-targeted therapy (eg, sorafenib, pazopanib, or sunitinib) for at least one (3 months) assessment period and attended multiple visits at the participating center during the study. Patients were excluded if they were pregnant, had HIV, or were enrolled in any other cancer clinical trial.

2.3. Baseline characteristics

Patients were characterized at baseline in terms of their demographics (eg, sex and age), anthropomorphic measures (eg, body weight and height), and clinical characteristics (eg, European Cooperative Oncology Group Performance Status, number of metastases and metastatic site[s], comorbidities, and prior anticancer treatment). Site of metastasis was classified within other sites if fewer than five patients had a metastasis at that particular location.

2.4. Outcomes

The primary objective of the study was to characterize real-world prescribing of subsequent (focusing on 2L) targeted therapy (sequence, use, and duration) in patients with mRCC who had received prior anti-VEGF therapy. Incidence, duration, and management of TRAEs were also characterized. TRAEs were identified through retrospective medical chart review and confirmed by the principal investigator (PI). A list of relevant AEs was developed a priori, and patient records were screened for related relief medications prescriptions and/or AE descriptions prior to PI validation. TRAE management was described in terms of required hospitalizations and/or relief medications, and their duration.

2.5. Statistical analyses

Descriptive statistics were used to characterize the study population, prescribing practices, and TRAEs (eg, mean standard deviation [SD], median [range], and number [percentage]).

3. RESULTS

3.1. Patient characteristics

Overall, 27 patients with mRCC were eligible for inclusion in the study (n = 21 from VGH-TPE and n = 6 from NTUH). The mean (SD) patient age was 63.1 (11.1) years, and the mean (SD) body weight was 66.7 (10.4) kg; 81.5% of patients were male (Table 1). Two-thirds (66.7%) of patients had been diagnosed with RCC for less than 1 year before initiating 1L targeted therapy. All patients (100.0%) received 1L sunitinib treatment, and all had metastases. Metastatic sites included the lungs (55.6%), bone (37.0%), adrenal gland (22.2%), lymph node (18.5%), and other (liver, peritoneal, or brain) sites (40.7% combined). The most common site of metastases was the lungs (55.6% of patients) followed by bones (37.0% of patients). The majority of patients (77.8%) had undergone prior nephrectomy.

3.2. Real-world treatment patterns

Median (minimum to maximum) duration of 1L sunitinib was 10 (1.8–65.8) months (Table 2). The most common reason for discontinuing 1L treatment was disease progression (88.9%; Fig. 1). The majority of patients (85.2%) received everolimus as their 2L treatment; only four patients (14.8%) received 2L axitinib (Table 1). Most patients receiving everolimus (91.3%) and 50% of patients receiving axitinib initiated therapy at a dose of 10 mg once daily (QD). All others started at a lower daily dose

Table 1

Patient characteristics at baseline

Characteristics	Overall (N = 27)
Demographic and anthropomorphic	
Male, n (%)	22 (81.5)
Age at 2L targeted therapy initiation, mean (SD)	63.1 (11.1)
Weight, kg; mean (SD)	66.7 (10.4)
Height, cm; mean (SD)	164.4 (7.2)
Clinical	
Time from RCC diagnosis to targeted therapy initiation,[a] n (%)	
<1	18 (66.7)
1–5	2 (7.4)
>5	7 (25.9)
Metastatic site,[b] n (%)	
Lungs	15 (55.6)
Bone	10 (37.0)
Adrenal gland	6 (22.2)
Lymph node	5 (18.5)
Other	11 (40.7)
Prior nephrectomy, n (%)	21 (77.8)
Prior kidney transplantation, n (%)	1 (3.7)
1L sunitinib therapy, n (%)[c]	27 (100.0)

1L = first line; 2L = second line; RCC = renal cell carcinoma.

[a]Based on RCC diagnoses at the study centre only.

[b]Patients could have more than one metastatic site.

[c]Includes 1 patient who received pazopanib prior to sorafenib for less than 1 mo; sunitinib was considered 1L treatment.

(Supplementary Figure 1, http://links.lww.com/JCMA/A130; Supplementary Table 1, http://links.lww.com/JCMA/A131). Median (range) duration was 4.0 (0.1–30.5) months of 2L everolimus and 4.2 (0.5–9.2) months for 2L axitinib treatment (Table 2). Disease progression was the most common reason for discontinuation of 2L therapy (44.4%), followed by poor performance status (25.9%; Fig. 1).

Table 2

2L targeted therapy treatment patterns for patients with renal cell carcinoma managed in routine care practice in Taiwan

		2L targeted therapy subgroup	
	Overall (n = 27)	Everolimus (n = 23)	Axitinib (n = 4)
Duration of 1L sunitinib, n (%)			
Mean (SD), mo	16.1 (15.7)	…	…
Median (min–max), mo	10 (1.8–65.8)	…	…
Duration of 2L therapy[a]			
Mean (SD), mo	6.7 (6.5)	7.5 (7.0)	4.5 (3.6)
Median (min–max), mo	3.4 (0.1–30.0)	4.0 (0.1–30.5)	4.2 (0.5–9.2)
Discontinued 2L targeted therapy, n (%)	27 (100.0)	23 (100.0)	4 (100.0)
Reasons for 2L discontinuation, n (%)[b]			
Disease progress	12 (42.9)	12 (50.0)	0 (0.0)
Poor PS	7 (25.0)	6 (25.0)	1 (25.0)
TRAEs	3 (10.7)	3 (12.5)	0 (0.0)
Patient decision	2 (7.1)	1 (4.2)	1 (25.0)
Unknown/NR	4 (14.3)	2 (8.3)	2 (50.0)

1L = first line; 2L = second line; max = maximum; min = minimum; NR = not reported; PS = performance status; TRAE = treatment-related adverse event.

[a]One patient remained on therapy at the end of the study period.

[b]One patient treated with everolimus discontinued 2L therapy owing to both disease progression and poor PS; therefore, a denominator of 24 has been used for the everolimus arm and 28 for the overall population.

3.3. Treatment-related adverse events

In total, 10 TRAEs were reported during the study among seven patients receiving everolimus (33.3%; Fig. 2). Two patients were hospitalized as a result of TRAEs: one for renal failure (length of stay [LOS], 44 days) and the other for interstitial pneumonitis (LOS, 17 days). The case of renal failure was managed with diuretics (42-day duration) and albumin treatment (8-day duration). The case of interstitial pneumonitis was managed with methylprednisolone (treatment duration, 1 day). Both hospitalizations resulted in discontinuing everolimus treatment (Fig. 2).

All other TRAEs (n = 7) were managed in the outpatient setting or by dose adjustment (n = 1). Five cases of treatment-emergent hypertension were identified by records of either newly initiated antihypertensive medication or dose increase of existing medication during the study period. One case of treatment-emergent hyperglycemia was recorded, which was managed by halving the daily dose of everolimus, from 10 to 5 mg QD.

4. DISCUSSION

This study characterizes a real-world population of patients receiving ≥2L treatment for mRCC at two of the largest hospitals in Taiwan between 2013 and 2017. We found that the majority of mRCC patients had undergone prior nephrectomy (77.8%) and all received 1L sunitinib therapy. Disease progression was the most common reason for discontinuation (88.9%). 2L everolimus was the most commonly prescribed therapy after 1L sunitinib (85.2% of patients); only 14.8% of patients included in the study received 2L axitinib. All of the TRAEs recorded during the study (n = 10) occurred in patients receiving everolimus. Most (8 of 10) TRAEs (5 cases of hypertension, 2 cases of hand-foot syndrome, and 1 incidence of hyperglycemia) were managed in the outpatient setting. Two TRAEs required hospitalization, one for renal failure and the other for interstitial pneumonitis. The findings offer insight into routine prescribing of targeted therapies for mRCC in Taiwan before the emergence of immune CPIs and may serve as a benchmark against which to characterize and assess subsequent practice changes and their implications.

The use of everolimus or axitinib as 2L therapy largely aligns with EAU guidance for RCC at the time of the study: 2L axitinib or everolimus for patients who have progressed despite prior VEGF-targeted therapy.[7] The predominant prescribing of 2L everolimus observed in this Taiwanese cohort likely reflects NHIA reimbursement policy over the period. In Taiwan, treatment with everolimus has been reimbursed for patients with mRCC after the failure of VEGF-targeted therapy since 2011, but axitinib has only been reimbursed since 2017 and is limited to patients with progressive mRCC after failing sunitinib or cytokine therapy.[13] Accordingly, the index date of treatment initiation suggests that axitinib was largely (in 3 of 4 patients) prescribed after it became eligible for NHIA reimbursement.

Owing to the small sample size of the present study and occurrence of no reported TRAEs in patients receiving axitinib, it was not possible to compare the profile of TRAEs associated with everolimus versus axitinib. Based on the tolerability data for patients receiving everolimus, however, the current study suggests that TRAEs during 2L everolimus seldom led to discontinuation and could generally be managed without the need for hospitalization. This finding echoes that of a retrospective evaluation of 2L everolimus in patients (n = 19) receiving routine care treatment for mRCC in Japan.[14] Only two of the 19 patients included in the Japanese study discontinued everolimus because of AEs, one because of severe acute kidney injury and the other because of grade 3 interstitial pneumonitis. No everolimus

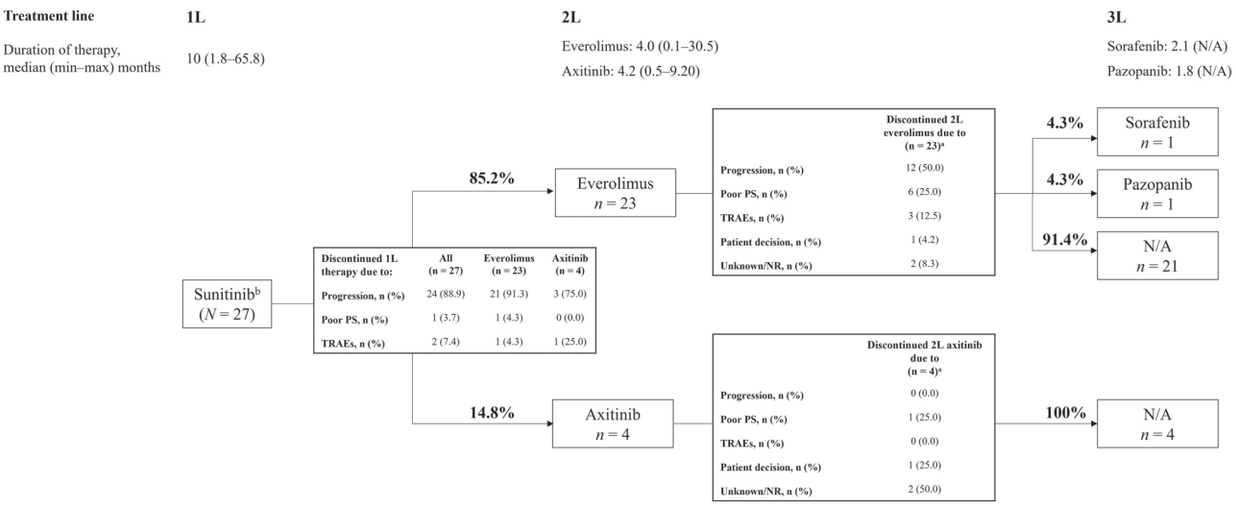

Fig. 1 Treatment pathway of targeted therapy in metastatic renal cell carcinoma routine care management in Taiwan. 1L = first line; 2L = second line; 3L = third line; max = maximum; min = minimum; N/A = not available; NR = not reported; PS = performance status; TRAE = treatment-emergent adverse event. [a]One patient reported two reasons for discontinuation: progression and poor PS; a denominator of 24 has been used for the everolimus arm. [b]One patient initiated 1L pazopanib but switched to sunitinib after less than 0.5 mo. Sunitinib was considered to be their first true 1L treatment.

patients experienced grade 3 or 4 hand-foot syndrome, and only 5% (n = 1) of patients experienced grade 3 or 4 hypertension.

Integration of data from assessments of real-world effectiveness–tolerability profiles as well as efficacy–safety profiles reported in randomized controlled trials (RCTs) will ultimately aid clinicians in their choice of 2L and ≥3L agents. In the phase 3 RECORD-1 trial of everolimus versus placebo in patients with mRCC who had progressed despite prior anti-VEGF therapy, everolimus significantly prolonged median PFS compared with placebo (4.9 versus 1.9 months, respectively; $p < 0.001$). No significant difference was observed in OS estimates. The most common serious AEs reported for patients receiving everolimus were infections (of all types, 10%), dyspnea (7%), and fatigue (5%).[15] In the phase 3 AXIS trial of 2L axitinib versus sorafenib following prior anti-VEGF inhibitor therapy (mTOR inhibitor or cytokine therapy), axitinib significantly prolonged PFS compared with sorafenib in patients with mRCC (6.7 versus 4.7 months, respectively; $p < 0.0001$). The most common AEs reported among patients receiving axitinib were diarrhea, hypertension, and fatigue; 4% (n = 14) of patients discontinued axitinib owing to treatment toxicity.[16] Currently, no prospective RCTs have compared 2L axitinib and everolimus directly.

Real-world management data are limited in RCC, especially in Taiwan. The present study provides insights into the profile of patients with mRCC managed in routine care in Taiwan, as well as common treatment approaches and their tolerability. The reasonably low number of patients eligible for inclusion in the study reflects the close involvement of the participating centers in trials of investigational drugs for RCC, and as a result, a high proportion of patients were ineligible for inclusion. In this study the percentage of male patients included was higher than the overall epidemiology of the disease. Nevertheless, the centers involved in the study are

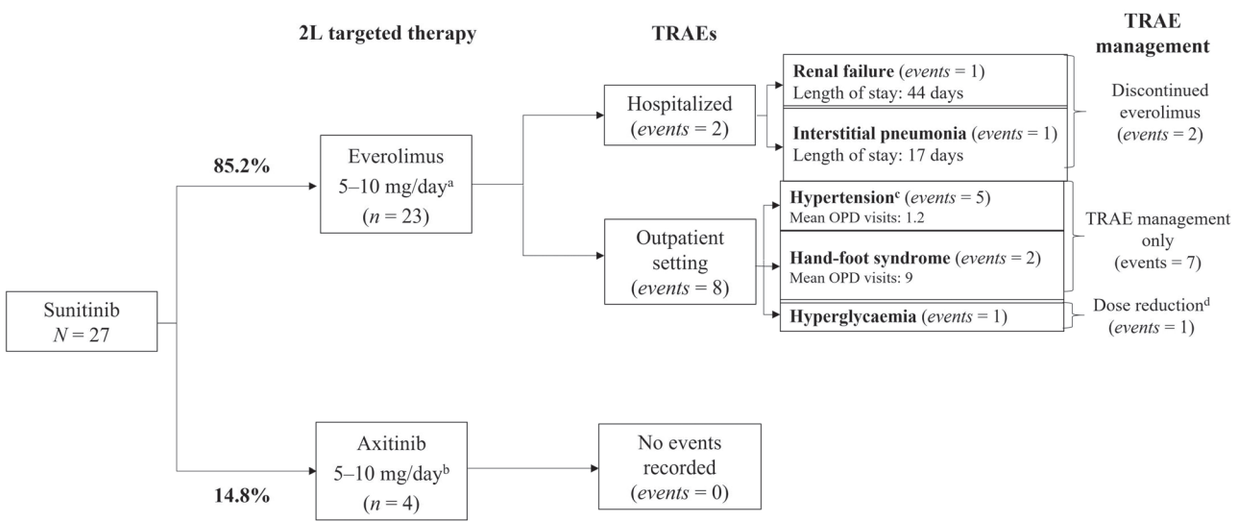

Fig. 2 Summary of treatment-related adverse events and required management by 2L therapy. 2L = second line; OPD = outpatient department; TRAE = treatment-emergent adverse event. [a]5 mg/twice a day (n = 1); 5 mg/d (n = 1); 10 mg/d (n = 21). [b]5 mg/d (n = 1); 7.5 mg/d (n = 1); 10 mg/d (n = 2). [c]Defined as initiation or increase in antihypertensive treatment during the period of 2L therapy. [d]Everolimus dose reduced from 10 to 5 mg daily.

among the three biggest hospitals in Taiwan and manage a substantial proportion of patients treated for RCC, nationally, and, therefore, the reported treatment patterns are likely to be in general representative of routine mRCC management practices in Taiwan.

While retrospective studies using electronic health records are limited by the prerecorded nature of the data and by the fact that they were recorded for the purposes of clinical management rather than research, the study team tried to mitigate against data shortfalls by undertaking manual checks for data completeness, accuracy and consistency, and protocol compliance. Despite these efforts, real-world data are subject to inherent limitations, such as selection bias and attrition bias, that should be considered when interpreting the results. An additional limitation is the small patient number eligible for inclusion in this study. Furthermore, the fact that sunitinib was the standard of care for 1L treatment, followed by 2L axitinib and everolimus, at the time of the study, meant that the study period predated the date of approval of newer generation TKIs and CPIs licensed for the treatment of patients with mRCC, potentially limiting the ability to extrapolate the findings to current practices. For instance, RCC management approaches have evolved since the time of the study. The current EAU guidance now recommends either combination CPI/TKI or CPI/CPI therapy as the 1L standard of care for patients with metastatic ccRCC, followed by 2L cabozantinib or nivolumab.[7,11] In patients who cannot receive or tolerate CPIs, the recommended alternative standard of care is sequential TKI monotherapy (1L and 2L).[7,11] In 2019, the NHIA reimbursement policy in Taiwan was also extended to include reimbursement of the CPI nivolumab (in April 2019) and the TKI cabozantinib (in December 2019).[13] In keeping with EAU-endorsed usage, cabozantinib is eligible for NIHA reimbursement in patients with mRCC who have received previous anti-angiogenic therapy. Reimbursement of nivolumab, however, is more restrictive than recommended in the EAU guidelines. Although the 2020/21 EAU guidelines recommend combination nivolumab/ipilimumab use as a 1L standard of care option in patients with intermediate and poor risk metastatic ccRCC, or as 2L monotherapy after 1L TKI treatment,[7,11] NIHA reimbursement is restricted to use in patients with ccRCC who have failed on two prior targeted therapies.[13] No CPI/CPI or CPI/TKI combination approaches for RCC are currently approved for reimbursement in Taiwan. Despite these changes in guidelines and reimbursement policy, the current analysis serves as a benchmark against which evolving management approaches can be evaluated.

In conclusion, this evaluation of real-world treatment patterns in patients with mRCC suggests that routine prescribing of ≥2L targeted therapies in Taiwan broadly aligned with international management guidelines and national reimbursement policy during the study period. No unexpected TRAEs were observed, and most TRAEs were managed in the outpatient setting. In the absence of prospective trials to determine the optimal treatment sequence for the management of patients with mRCC, evidence from real-world studies can help to inform clinical decision-making.

APPENDIX A. SUPPLEMENTARY DATA

Supplementary data related to this article can be found at http://links.lww.com/JCMA/A130 and http://links.lww.com/JCMA/A131.

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