Recommendations for the management of advanced and metastatic renal cell carcinoma: joint consensus statements from the Hong Kong Urological Association and the Hong Kong Society of Uro-Oncology

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ABSTRACT

Introduction: Kidney cancer, primarily renal cell carcinoma (RCC), ranks among the top 10 most common malignancies in the male population of Hong Kong. In 2019, members of two medical societies in Hong Kong formed an expert panel to establish a set of consensus statements for the management of metastatic RCC. On 22 June 2021, the same panel met to review recent evidence and reassess their positions regarding the management of advanced and metastatic RCC, with the aim of providing recommendations for physicians in Hong Kong.

Participants: The panel included 12 experts (6 clinical oncologists and 6 urologists) who had extensive experience managing patients with RCC in Hong Kong.

Evidence: The panel reviewed randomised controlled trials, observational studies, systematic reviews/meta-analyses, and international clinical guidelines to address key clinical questions that were identified before the meeting.

Consensus Process: In total, 15 key clinical questions were identified before the meeting, covering the surgical and systemic treatment of advanced or metastatic clear cell, sarcomatoid, and non-clear cell RCCs. At the meeting, the panellists voted on these questions, then discussed relevant evidence and practical considerations.

Conclusions: The treatment landscape for advanced and metastatic RCC continues to evolve. More immune checkpoint inhibitor (ICI)–based combination regimens will be indicated for the treatment of metastatic clear cell RCC. There is increasing evidence concerning the benefit of adjuvant ICI treatment for resected advanced RCC. This article summarises recent evidence and expert insights regarding a series of key clinical questions about the management of advanced and metastatic RCC.

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Introduction

In 2018, kidney cancer was the ninth most common malignancy in the male population of Hong Kong, with a relative frequency of 3%.[1] The predominant type of kidney cancer is renal cell carcinoma (RCC), which mainly comprises the clear cell subtype; non-clear cell RCC can be subdivided into papillary, chromophobe, and other rarer forms (eg, collecting duct).[2] Many RCCs are found incidentally without symptoms suggestive of malignancy; approximately 30% of patients have metastatic disease at the time of diagnosis.[2]

The management of advanced and metastatic RCC has been transformed by the development of vascular endothelial growth factor receptor tyrosine kinase inhibitors (TKIs) and, more recently, immune checkpoint inhibitors (ICIs). In 2019, members of two medical societies in Hong Kong formed an expert panel to establish a set of consensus statements for the management of metastatic RCC.[3] Since then, the treatment landscape has continued to change with the addition of two evidence-based ICI-TKI

晚期及轉移性腎細胞癌的治療建議：香港泌尿外科學會和香港泌尿腫瘤科學會聯合共識聲明

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引言：腎癌大多是腎細胞癌（RCC），是香港男性最常見的十大癌症之一。2019年，香港兩個醫學組織組成專家小組，就轉移性RCC的治療制定共識聲明。2021年6月22日，專家小組在會議中審查近年證據，並重新評估他們對晚期及轉移性RCC治療的立場，旨在為香港醫生提供建議。

參與者：該小組包括12名專家（6名臨床腫瘤科醫生和6名泌尿科醫生），他們在治療香港RCC 患者方面擁有豐富經驗。

證據：專家組審查隨機對照試驗、觀察性研究、系統綜述 / 薈萃分析以及國際臨床指南，以解決會議前確定的關鍵臨床問題。

共識過程：會議前共確定15個關鍵臨床問題，涵蓋晚期或轉移性透明細胞、肉瘤樣和非透明細胞RCC的手術和全身治療。與會者就這些問題進行投票，然後就相關證據和實際考慮進行討論。

結論：晚期和轉移性RCC的治療前景不斷發展。更多基於免疫檢查點抑製劑（ICI）的聯合方案將用於治療轉移性透明細胞RCC。越來越多證據表明輔助ICI治療對切除晚期RCC的益處。本文總結有關晚期和轉移性RCC治療的一系列關鍵臨床問題的最新證據和專家見解。

combination therapies: nivolumab/cabozantinib and pembrolizumab/lenvatinib.[4,5] There is also increasing research concerning the role of adjuvant ICI in the treatment of advanced RCC after nephrectomy.[6] Considering these advances, the same expert panel met to review recent evidence and reassess their positions regarding the management of advanced and metastatic RCC through panel votes on a series of key clinical questions, with the aim of providing treatment recommendations for physicians in Hong Kong.

Methods

The meeting was held on 22 June 2021; the expert panel included 12 clinicians (6 clinical oncologists and 6 urologists) who had extensive experience managing patients with RCC in the public or private healthcare sectors. Prior to the meeting, the panel identified 15 key clinical questions (online supplementary Appendix) regarding the surgical and systemic treatment of advanced or metastatic clear cell, sarcomatoid, and non-clear cell RCCs in various risk categories. The panel reviewed randomised controlled trials, observational studies, systematic reviews/meta-analyses, and international clinical guidelines that addressed these clinical questions. Prior to the meeting, review materials had been identified through a search of the PubMed database for publications from January 2020 to May 2021 using the key words 'metastatic/advanced + renal cell carcinoma'; the search results were supplemented with additional articles solicited by the panellists. At the meeting, the panellists voted on the 15 questions, then discussed relevant clinical evidence and practical considerations for real-world clinical practice. The full voting record for each question is provided in the online supplementary Appendix.

Results

First-line systemic therapies for clear cell metastatic renal cell carcinoma

Current published evidence

To decide on a treatment strategy for clear cell metastatic RCC, the International Metastatic RCC Database Consortium (IMDC) risk category[7] remains a key consideration. Current international guidelines largely recommend ICI-containing combination treatment as the standard of care for metastatic RCC in all IMDC risk categories (Table 1).[8,9] In phase III open-label randomised trials, the recommended ICI-containing regimens significantly improved progression-free survival (PFS), overall survival (OS), and objective response rates (ORRs), when compared with sunitinib as first-line treatment for metastatic RCC in the respective primary study populations: for intermediate/poor-risk patients, ipilimumab/nivolumab[10]; and for intention-to-treat patients, pembrolizumab/axitinib,[11] nivolumab/cabozantinib,[4] and pembrolizumab/lenvatinib[5] (Table 2). Post-hoc analyses showed that ipilimumab/nivolumab and nivolumab/cabozantinib were associated with better health-related quality of life compared with sunitinib[12,13]; there were no significant differences in health-related quality of life between sunitinib and pembrolizumab/axitinib or between sunitinib and pembrolizumab/lenvatinib.[14,15]

Recommendations from the expert panel

Based on the available evidence and insights from the expert panel, ICI-ICI (ie, ipilimumab/nivolumab) and ICI-TKI combinations each have specific advantages and disadvantages (Table 3[4,5,10,11]), which should be considered when selecting a treatment regimen.

According to the panel consensus, the IMDC risk category and burden of disease or presence of symptoms were regarded as the most important patient/disease factors when selecting the first-line treatment regimen for advanced or metastatic clear cell RCC. Efficacy (primarily OS, followed by PFS and ORR) and toxicity were regarded as the most important treatment-related factors when selecting a treatment regimen. Figure 1 illustrates the treatment algorithm recommended by the panel.

TABLE 1. Guideline-recommended first-line treatments for clear cell metastatic renal cell carcinoma

IMDC risk category	NCCN guidelines[8]		EAU guidelines[9]	
	Preferred regimens	Other recommended regimens	Standard of care	Alternative for patients who cannot receive or tolerate ICIs
Favourable	Pembrolizumab/axitinib Nivolumab/cabozantinib Pembrolizumab/lenvatinib Pazopanib Sunitinib	Avelumab/axitinib Cabozantinib Ipilimumab/nivolumab	Pembrolizumab/axitinib Nivolumab/cabozantinib Pembrolizumab/lenvatinib	Sunitinib Pazopanib
Intermediate/poor	Pembrolizumab/axitinib Nivolumab/cabozantinib Pembrolizumab/lenvatinib Ipilimumab/nivolumab Cabozantinib	Avelumab/axitinib Pazopanib Sunitinib	Pembrolizumab/axitinib Nivolumab/cabozantinib Pembrolizumab/lenvatinib Ipilimumab/nivolumab	Cabozantinib Sunitinib Pazopanib

Abbreviations: EAU = European Association of Urology; ICIs = immune checkpoint inhibitors; IMDC = International Metastatic RCC Database Consortium; NCCN = National Comprehensive Cancer Network

TABLE 2. Efficacy outcomes of immune checkpoint inhibitor–based regimens from phase III open-label randomised trials

	CheckMate 214[10] (intermediate/poor-risk patients)		KEYNOTE-426[11] (ITT population)		CheckMate 9ER[4] (ITT population)		CLEAR[5] * (ITT population)	
	Ipilimumab/ nivolumab	Sunitinib	Pembrolizumab/ axitinib	Sunitinib	Nivolumab/ cabozantinib	Sunitinib	Pembrolizumab/ lenvatinib	Sunitinib
Median PFS, mo	11.6	8.3	15.7	11.1	16.6	8.3	23.9	9.2
HR (95% CI)	0.75 (0.62-0.90); P=0.0015		0.68 (0.58-0.80); P<0.0001		0.51 (0.41-0.64); P<0.001		0.39 (0.32-0.49); P<0.001	
Median OS, mo	47.0	26.6	45.7	40.1	Not reached (median follow-up, 18.1 mo)		Not reached (median follow-up, 26.6 mo)	
HR (95% CI)	0.66 (0.55-0.80); P<0.0001		0.73 (0.60-0.88); P<0.001		0.60; 98.89% CI=0.40-0.89; P=0.001		0.66 (0.49-0.88); P=0.005	
ORR, %	42.1	26.3	60.4	39.6	55.7	27.1	71.0	36.1
CR rate, %	10.1	1.4	10	3.5	8.0	4.6	16.1	4.2

Abbreviations: CI = confidence interval; CR = complete remission; HR = hazard ratio; ITT = intention-to-treat; ORR = objective response rate; OS = overall survival; PFS = progression-free survival

* Patients were randomly assigned to receive pembrolizumab/lenvatinib, everolimus/lenvatinib, or sunitinib; data regarding everolimus/lenvatinib treatment are not shown here

TABLE 3. Expert panel opinions concerning immune checkpoint inhibitor–immune checkpoint inhibitor and immune checkpoint inhibitor–tyrosine kinase inhibitor combinations

	ICI + ICI	ICI + TKI
OS/PFS benefits	Neither OS nor PFS benefits in favourable-risk patients	Both OS and PFS benefits offered in ITT populations
Objective response rate	Lower (42.1%)[10]	Higher (55.7%-71.0%)[4,5,11]
Durability of response	Durable (for responders)	Not yet determined
Safety profiles	No TKI-related AEs	Chronic TKI-related AEs
	Higher risk of immune-related AEs	Lower risk of immune-related AEs
	Higher probability of needing high-dose steroids	Lower probability of needing high-dose steroids
Quality of life	May be better	May be worse
Potential for stopping treatment	Some intermediate/poor-risk patients could remain progression-free after treatment discontinuation (because the PFS curve plateaued after 30 months in CheckMate 214)[10]	Long-term use of dual drugs
Treatment cost	Lower (because patients receive long-term ICI monotherapy)	Higher (because of long-term use of dual drugs)

Abbreviations: AE = adverse event; ICI = immune checkpoint inhibitor; ITT = intention-to-treat; OS = overall survival; PFS = progression-free survival; TKI = tyrosine kinase inhibitor

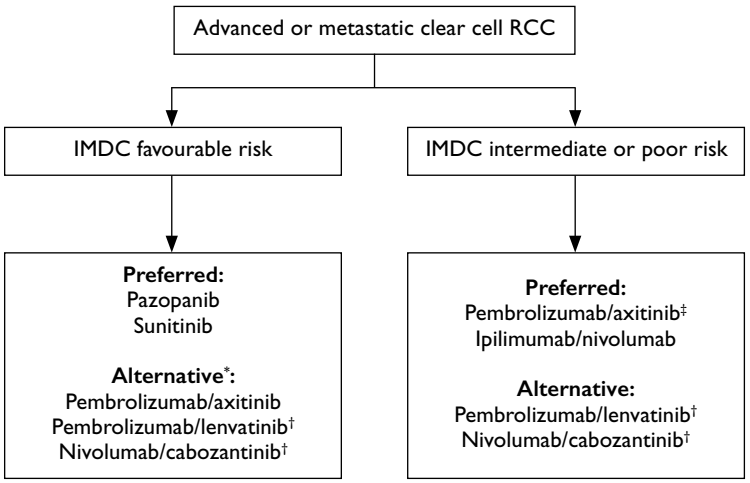

FIG 1. Expert panel recommendations of systemic first-line treatment regimens for advanced or metastatic clear cell renal cell carcinoma

Abbreviations: IMDC = International Metastatic RCC Database Consortium; RCC = renal cell carcinoma

* Combination treatment should be considered for patients with extensive or symptomatic disease

† More experience in Hong Kong should be accumulated

‡ Preferred in patients with clinically significant symptoms and extensive disease

For IMDC favourable-risk advanced or metastatic clear cell RCC, TKI monotherapy (pazopanib or sunitinib) was regarded as the preferred treatment regimen. In subgroup analyses of phase III open-label randomised trials, the OS benefits of ICI-TKI combinations were uncertain in favourable-risk patients, but these results should be interpreted cautiously because the numbers of participants were limited in each subgroup.[4,5,16] Despite the uncertain OS benefits, ICI-TKI combinations provided significant PFS and ORR benefits compared with sunitinib; therefore, they may remain useful in favourable-risk patients, particularly patients with extensive or symptomatic disease who desire treatment with a higher ORR.

For IMDC intermediate/poor-risk advanced or metastatic clear cell RCC, ICI-based combination treatment (preferably pembrolizumab/axitinib or ipilimumab/nivolumab) is recommended. In patients with clinically significant symptoms and extensive disease, pembrolizumab/axitinib may be preferred because it appeared to offer stronger antitumour activity (ORR, 60.4%; stable disease rate, 22.9%; progressive disease rate, 11.3%) compared with ipilimumab/nivolumab, according to the KEYNOTE-426 study.[11] In the CheckMate 214 study, approximately 20% of patients experienced disease progression after treatment with ipilimumab/nivolumab.[10]

With respect to newer ICI-TKI combinations (ie, pembrolizumab/lenvatinib and nivolumab/cabozantinib), there is a need to accumulate additional experience in Hong Kong. The optimal dose and tolerability profile of lenvatinib, particularly in Asian patients, should be further investigated; in the CLEAR study, 70% of patients required dose reductions for lenvatinib.[5] For cabozantinib, there is a lack of flexibility in dose manipulation; only 60 mg, 40 mg, and 20 mg were available for use in the CheckMate 9ER study.[4] In contrast, the dosage of axitinib is readily adjustable; 1-mg increments or reductions can be implemented depending on patient tolerability.

In public hospitals in Hong Kong, ICIs for the treatment of RCC remain self-financed, whereas TKI monotherapy (ie, axitinib, pazopanib, and sunitinib) is supported by the Safety Net programme.[17]

Adjuvant treatment after nephrectomy in patients with advanced renal cell carcinoma

Current evidence regarding adjuvant pembrolizumab treatment

Nephrectomy is the standard of care for localised RCC; however, patients with advanced RCC are at risk of disease recurrence, and thus the use of adjuvant treatment warrants investigation. In the KEYNOTE-564 phase III trial, patients with high-risk, fully resected clear cell RCC (M0 or M1 without evidence of disease) were randomised to receive adjuvant pembrolizumab or placebo.[6] At the median follow-up interval of 24 months, adjuvant pembrolizumab significantly improved disease-free survival compared with placebo (77.3% vs 68.1% at 24 months; hazard ratio [HR]=0.68, 95% confidence interval [CI]=0.53-0.87; P=0.002 [two-sided]). While the OS data were immature, there was a trend in favour of adjuvant pembrolizumab (96.6% vs 93.5% at 24 months; HR=0.54; 95% CI=0.30-0.96). These results suggest that adjuvant pembrolizumab can prevent relapse after surgery in patients with advanced RCC.

Recommendations from the expert panel

The panellists noted that the use of adjuvant systemic treatment after nephrectomy depends on patient preference after a discussion of the benefits and risks. The limitations of adjuvant treatment include the lack of clear markers of efficacy, the risks of overtreatment and toxicity (particularly in older and frailer patients), and the potential for fewer available treatment regimens in patients who experience disease recurrence. Compared with adjuvant TKI, adjuvant ICI may be associated with fewer adverse effects and better quality of life, offering new treatment opportunities for high-risk patients (eg, with nodal metastases). Further studies are needed to investigate the clinical benefit of adjuvant ICI

in distinct patient subgroups (eg, patients with non-clear cell RCC or bone oligometastases) and to explore a risk-adapted approach for optimising patient selection.

Treatment remains investigational for patients who develop metastatic disease after receiving adjuvant pembrolizumab. The panellists favoured TKI monotherapy (pazopanib or sunitinib), particularly for patients with a short relapse-free period (eg, <6 months) after adjuvant pembrolizumab treatment. They noted that patients with a longer relapse-free period may receive ICI-based combination treatment; for example, the antitumour activity of pembrolizumab/lenvatinib in ICI-pre-treated patients with clear cell metastatic RCC (ORR, 55.8%) was demonstrated in a phase I/IIb study.[18]

Treatment for advanced or metastatic renal cell carcinoma with sarcomatoid de-differentiation

The standard of care for sarcomatoid RCC has not been determined. Consistent with the previous consensus statement, the panellists favoured an ICI-containing combination for the treatment of metastatic RCC with sarcomatoid de-differentiation, which is generally within the IMDC intermediate/poor-risk category. Compared with other RCCs that lack sarcomatoid features, sarcomatoid RCCs have higher programmed death-ligand 1 expression; thus, they may be more responsive to ICI immunotherapies.[19] In subgroup analyses of phase III randomised studies, ICI-containing regimens offered OS, PFS, and ORR benefits compared with sunitinib in patients who had metastatic RCC with sarcomatoid de-differentiation.[20] Phase III randomised trials dedicated to the treatment of sarcomatoid RCC are expected.

Cytoreductive nephrectomy

Consistent with the previous consensus statement, the panellists favoured systemic treatment, rather than upfront cytoreductive nephrectomy (CN), for the management of de novo metastatic RCC.

The CN candidacy in IMDC favourable-risk patients remains unclear, particularly in the ICI era. Several panellists noted that CN may be irrelevant to this patient population because most will have already undergone nephrectomy or decided to avoid nephrectomy based on age and performance status, considering that the time from their diagnosis until systemic treatment is ≥1 year. However, when immediate systemic treatment is not required, upfront CN with metastasectomy may be considered for patients with asymptomatic primary tumours and limited metastases confined to the lung. There is also preliminary evidence to support the use of CN combined with ICI immunotherapy in patients with pathologically favourable tumour characteristics. An analysis of the United States National Cancer Database found that, in patients with metastatic RCC, the combination of CN (primarily in the upfront setting) and ICI immunotherapy improved median OS (not reached vs 11.6 months; HR=0.23, P<0.001) compared with ICI immunotherapy alone.[21] Because ICI-based combination treatment is increasingly used, the role and sequence of CN warrant prospective validation.

The panellists recommended deciding whether to perform CN in IMDC intermediate-risk patients based on the extent of disease and symptoms. Upfront CN may be considered for patients with solitary or limited metastases (oligometastases). Otherwise, delayed CN may be considered for patients who respond well to systemic treatment. Further studies are required to explore the patient selection and optimal timing for CN in the context of ICI immunotherapy.

The panellists recommended avoiding CN in IMDC poor-risk patients, considering their low life expectancy (7-8 months) and poor prognosis, as well as the potential for surgical complications and impacts on quality of life. Retrospective data from the IMDC demonstrated that poor-risk patients did not experience survival benefits from CN.[22]

Treatment for advanced or metastatic non-clear cell renal cell carcinoma

The standard of care for metastatic non-clear cell RCC remains unclear, particularly considering the heterogeneity among subtypes. Based on the current evidence, the panellists favoured TKI monotherapy (cabozantinib or sunitinib). In a randomised open-label phase II trial, patients with metastatic papillary RCC were randomly assigned to receive sunitinib, cabozantinib, crizotinib, or savolitinib; only cabozantinib improved median PFS compared with sunitinib (9.0 vs 5.6 months; HR=0.60 [95% CI=0.37-0.97], one-sided P=0.019).[23] The antitumour activity of sunitinib in metastatic non-clear cell RCC has been demonstrated in prospective studies.[24,25]

Subsequent treatment for advanced or metastatic clear cell renal cell carcinoma after progression on first-line systemic treatment

While the optimal sequence of treatment remains unclear, the principle of choosing a subsequent treatment (Fig 2) is consistent with the previous consensus statement. In patients who demonstrated progression after ICI-based combination treatment, the panellists favoured TKI monotherapy, primarily cabozantinib; its antitumour activity in patients with prior exposure to ICIs has been demonstrated

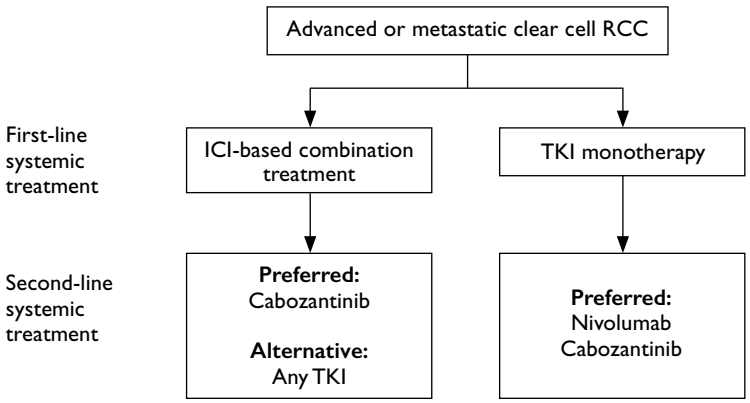

FIG 2. Expert panel recommendations of second-line treatment regimens for advanced or metastatic clear cell renal cell carcinoma
Abbreviations: ICI = immune checkpoint inhibitor; RCC = renal cell carcinoma; TKI = tyrosine kinase inhibitor

in large retrospective studies.[26,27] In patients who demonstrated progression after first-line TKI monotherapy, the panellists favoured nivolumab or cabozantinib based on prospective evidence,[28,29] which was described in the previous consensus statement.

Conclusions

The treatment landscape for advanced and metastatic RCC is evolving. More ICI-based combination regimens have recently been shown to offer survival benefits, compared with TKI monotherapy, as first-line systemic treatment in patients with metastatic clear cell RCC. There is increasing evidence to support the feasibility of adjuvant ICI treatment after surgery in patients with advanced RCC. This article has summarised recent evidence and insights from an expert panel on a series of key clinical questions, with the goal of optimising the management of advanced and metastatic RCC in Hong Kong. These recommendations are expected to undergo regular review and updating, considering that several crucial areas (eg, the role of CN combined with ICI-based treatment, the standard of care for RCCs with sarcomatoid features or non-clear cell histology, and the optimal sequence of systemic treatments) require further investigation.

Author contributions

All authors contributed to the concept and/or design of the study, acquisition of the data, analysis and/or interpretation of the data, drafting of the manuscript, and critical revision of the manuscript for important intellectual content. All authors have had full access to the data, contributed to the study, approved the final version for publication, and take responsibility for its accuracy and integrity.

Conflicts of interest

All authors have disclosed no conflicts of interest.

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