Original Article

Singapore Cancer Network (SCAN) Guidelines for Systemic Therapy of Metastatic Renal Cell Carcinoma (mRCC)

The Singapore Cancer Network (SCAN) Genitourinary Cancer Workgroup

Abstract

Introduction: The SCAN genitourinary cancer workgroup aimed to develop Singapore Cancer Network (SCAN) clinical practice guidelines for systemic therapy of metastatic renal cell carcinoma (mRCC). Materials and Methods: The workgroup utilised a modified ADAPTE process to calibrate high quality international evidence-based clinical practice guidelines to our local setting. Results: Six international guidelines were evaluated—those developed by the National Comprehensive Cancer Network (2014), the European Association for Urology (2013), the European Society of Medical Oncology (2012), the National Institute of Health and Clinical Excellence (2011), the Canadian Kidney Cancer Forum (2013) and the Asian Oncology Summit (2012). Recommendations on the first-, second- and third-line treatment for mRCC were developed. Conclusion: These adapted guidelines form the SCAN Guidelines 2015 for systemic therapy of mRCC.

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Key words: Kidney cancer, Recommendations, Singapore

Introduction

Kidney cancer accounts for less than 1% of all cancers. There are over 200,000 new cases diagnosed with renal cell carcinoma (RCC) and over 100,000 deaths a year worldwide. It is slightly more common in men than in women, and is mainly detected in people in their middle age. In Singapore, kidney cancer (together with other urothelial cancers) ranks as the 9th most common cancer in males.[1]

Since 2005, a number of new targeted agents have come into the local market for the treatment of this disease. With many of these therapies showing promising outcomes with improved progression-free survival (PFS) and overall survival (OS), it is important to discuss the timing, and sequencing of these drugs, specifically in the local setting.

The SCAN Guidelines for Systemic Therapy of Metastatic Renal Cell Carcinoma

The SCAN Guidelines are clinical practice guidelines for the front-line systemic treatment of newly diagnosed metastatic renal cell carcinoma (mRCC).

These first edition guidelines are intended to serve as treatment recommendations by members of this working group regarding their views on current existing international guidelines for the management of mRCC. While it hopes to harmonise the management of this disease, it is not intended to serve as the standard of care or to replace good clinical judgment and the individualisation of treatments.

Target Users of the Guidelines

The guidelines will be of interest to oncologists, oncology nurse specialists, pharmacists, allied health workers and general practitioners involved in the management of men and women with mRCC.

Guideline Recommendations/Development

The SCAN Genitourinary Cancer Workgroup comprises a panel of 7 medical oncologists from Singapore with special interests in the management of kidney cancer. Membership of the workgroup was by invitation. The workgroup elected its own chairperson and decided on its own scope.

Address for Correspondence: Dr Ravindran Kanesvaran, Department of Medical Oncology, National Cancer Centre Singapore, 11, Hospital Drive, Singapore 169610.
Email: Ravindran.Kanesvaran@nccs.com.sg

Guideline selection was conducted through workgroup consensus. Potential conflicts of interest were declared by the International Committee of Medical Journal Editors (ICMJE) guidelines. Secretarial support for the overall guideline development effort was provided by Annals, Academy of Medicine Singapore. No other financial support was obtained. Guideline searching was conducted by the section lead with input from the workgroup members. The group met once in person, and completed guideline development through email communication.

The ADAPTE framework[2] was used as a pragmatic structure and guidance for calibration of international high quality guidelines to the Singapore context. The framework involves 3 phases: set-up, adaptation and finalisation. During the set-up phase, available resources were considered. During the adaptation phase, high quality guidelines were selected for evaluation and structured approaches developed for guideline evaluation and selection. This involved the extraction of data on source guideline development, the setting up of mechanisms for selecting recommendations and also recognising possible dissent amongst panel members. Calibration of guidelines to the local context based on available Singapore data was encouraged. The finalisation phase involved writing, external review, stakeholder feedback, and the setting up of a mechanism for regular updating. For each individual recommendation, agreement was established by a simple majority for established international recommendations and by a two-third majority for independent local recommendations. Dissenting workgroup members were invited to include comments for each recommendation. International measures of cost-effectiveness for each recommendation were obtained where available but not used to inform the recommendations.

These guidelines set out to address the 3 main management issues which were selected for this topic:

1. First-line Treatment of mRCC
2. Second-line Treatment of mRCC
3. Third-line Treatment of mRCC

Six international guidelines were selected for review (Supplementary Table 1):

- "NCCN Clinical Practice Guidelines Version 2.2014 Kidney Cancer" by the National Comprehensive Cancer Network (NCCN, USA)[3]
- "Guidelines on Renal Cell Carcinoma" by the European Association for Urology (EAU), 2013[4]
- "Renal Cell Carcinoma: ESMO Clinical Practice Guidelines for Diagnosis, Treatment and Follow-up" by the European Society for Medical Oncology (ESMO), 2012[5]
- "Management of Advanced Kidney Cancer: Canadian Kidney Cancer Forum 2013 Consensus Update" from the Canadian Kidney Cancer Forum, 2013[6]
- National Institute for Health and Care Excellence (NICE) Guidance:
  - Technology Appraisal Guidance 169. Sunitinib for the First-line Treatment of Advanced and/or Metastatic Renal Cell Carcinoma[7]
  - Technology Appraisal Guidance 178. Bevacizumab (First-line), Sorafenib (First- and Second-line), Sunitinib (Second-line) and Temsirolimus (First-line) for the Treatment of Advanced and/or Metastatic Renal Cell Carcinoma[8]
  - Technology Appraisal Guidance 215. Pazopanib for the First-line Treatment of Advanced Renal Cell Carcinoma[9]
  - Technology Appraisal Guidance 219. Everolimus for the Second-line Treatment of Advanced Renal Cell Carcinoma[10]
- "Management of Kidney Cancer in Asia: Resource-stratified Guidelines" from the Asian Oncology Summit, 2012[11]

These guidelines will be reviewed or updated every 2 years. If there are significant new developments that impact the management of mRCC, it will be reviewed earlier.

1. First-line Treatment of mRCC

First-line Treatment for Clear Cell mRCC

A number of first-line treatments have been approved and endorsed in many of the above international guidelines for use in clear cell mRCC patients based mainly on the Memorial Sloan Kettering Cancer Centre (MSKCC) prognostication criteria.[12] Here is the list of drugs approved and data to support its use. We have also included the NICE Incremental Cost Effectiveness Ratio (ICER) data to give an idea about the estimated relative cost-effectiveness of such drugs in the United Kingdom as there are no equivalent data in the local setting.

Sunitinib

Sunitinib was approved for use in the first-line based on the study by Motzer et al comparing it to interferon-alpha (IFN-α).[13] It is indicated for patients with good and intermediate MSKCC prognostic risk.[12] Median OS was greater in the sunitinib group than in the IFN-α group (26.4 vs 21.8 months, respectively; hazard ratio [HR] = 0.821; 95% CI, 0.673 to 1.001; $P = 0.051$) per the primary analysis of unstratified log-rank test ($P = 0.013$ per unstratified Wilcoxon test). By stratified log-rank test, the HR was 0.818

(95% CI, 0.669 to 0.999; $P = 0.049$).[14] The true benefit of sunitinib was likely more if not for the crossover allowed for in the study for patients who had progressed on IFN-α.

Pazopanib

Pazopanib was approved for use in the first-line in patients with MSKCC good and intermediate risk based on the study by Sternberg et al, comparing it to placebo.[15] The difference in final OS between pazopanib- and placebo-treated patients was not statistically significant (22.9 vs 20.5 months, respectively; HR = 0.91; 95% CI, 0.71 to 1.16; one-sided $P = 0.224$). Early and frequent crossover from placebo to pazopanib and prolonged duration of crossover treatment confounded the OS analysis.[16] In a recent study comparing sunitinib and pazopanib, pazopanib was found to be non-inferior to sunitinib.[17]

The base-case ICERs for pazopanib (including a 12.5% discount on the list price) compared with best supportive care, IFN-α and sunitinib were USD $50,702, $59,767 and $2750 per quality-adjusted life year (QALY) gained, respectively.[9]

Temsirolimus

Temsirolimus was approved for use in the first-line setting specifically for MSKCC poor risk patients as defined by the poor risk criteria set by Hudes and team in that study.[18] Patients who received temsirolimus alone had longer OS (HR = 0.73; 95% CI, 0.58 to 0.92; $P = 0.008$) and PFS ($P < 0.001$) than did patients who received interferon alone. OS in the combination-therapy group did not differ significantly from that in the interferon group (HR = 0.96; 95% CI, 0.76 to 1.20; $P = 0.70$). Median OS in the interferon group, the temsirolimus group, and the combination-therapy group were 7.3, 10.9, and 8.4 months, respectively.[18] The indirect comparison of temsirolimus with best supportive care produced an ICER of USD $124,781 per QALY gained.[8]

Bevacizumab and Interferon

Bevacizumab and interferon combination have been approved in the first-line setting for MSKCC good and intermediate risk patients.[19,20] A total of 732 patients were enrolled. The median OS was 18.3 months (95% CI, 16.5 to 22.5) for bevacizumab plus IFN-α and 17.4 months (95% CI, 14.4 to 20.0) for IFN-α monotherapy (unstratified log-rank $P = 0.097$). Adjusting on stratification factors, HR was 0.86 (95% CI, 0.73 to 1.01; stratified log-rank $P = 0.069$) favouring bevacizumab plus IFN-α.[20]

The comparison of bevacizumab plus IFN-α with IFN-α plus placebo produced a base-case ICER of USD $115,241 per QALY gained.[8] In Singapore, this combination is rarely used in view of the cost and toxicities related to its use.

High-dose Interleukin-2 (IL-2)

High-dose IL-2 can be used in a selected group of fit clear cell mRCC patients postnephrectomy with limited disease burden.[21,22] Median duration for all complete responses has not yet been reached, but was at least 80 months (range, 7-131 months) at the time of this analysis. Median duration for all partial responses remains 20 months (range, 3-126 months). Median survival time for all 255 patients remains 16.3 months, with 10% to 20% of patients estimated to be alive 5 to 10 years after treatment with high-dose IL-2.[22]

Active Surveillance

Observation after cytoreductive nephrectomy is an option that can be considered in a selected group of asymptomatic clear cell mRCC patients.[23] In this local study, 15 patients were put on active surveillance. At a median follow-up of 18 months, 80% of patients had progressed. However, a third of the patients had at least 6 months of progression-free interval, and 3 of 15 patients had not progressed at prolonged follow-up durations of 18, 23, and 46 months. A third of the patients remained alive and the median survival for the cohort was 25 months. Preoperative predictive factors for non-progression after debulking nephrectomy included absence of abnormal laboratory indices, single organ system metastases, and good performance status. A recent study of 52 patients by Rini et al also showed that a selected group of mRCC patients can be safely observed before any treatment is started.[24]

First-line Treatment of Non-Clear Cell mRCC

No standard treatment is available and the patient should be treated in the framework of clinical trials if available. A number of recent randomised studies have shown that vascular endothelial growth factor (VEGF) tyrosine kinase inhibitors (TKI) like sunitinib may be better than everolimus in treating these patients and are hence a reasonable option for these patients.[25,26] Best supportive care can be offered as a reasonable option if the patient is not fit to receive further treatment.

Recommendations for First-line Treatment of mRCC

All the committee members who voted expressed preference for the Canadian guideline (Supplementary Table 1) because they listed clinical trials as the first option, followed by patient stratification by MSKCC, and they included observation as an option for first-line. All committee members agreed that tivozanib should not be a part of the local guidelines as data did not support its use.

For MSKCC Poor Risk Patients

It was noted that temsirolimus and sunitinib have both demonstrated their effectiveness in poor risk patients in clinical trials. Majority in the group (86%) held the opinion that pazopanib can be given to poor risk patients because of its better tolerability. One member (14%), however, disagreed, in view of the poor data supporting its use in poor risk patients. The member further elaborated that low-dose sunitinib[27] has a higher evidence of efficacy in poor risk patients. In the end, the majority (86%) voted to list pazopanib as a first-line option for poor risk patients, with an indication to mention the lack of strong level of evidence to it, and that pazopanib should only be used as an alternative to sunitinib. All members (100%) agreed everolimus should not be recommended as a first-line drug in poor risk patients. There was a unanimous vote to leave out the Asian resource-stratified guideline as it was broad and not relevant to our local setting (Table 1).

For Non-Clear Cell RCC (CCRCC) Patients

The committee noted that the Canadian guideline did not comment on non-CCRCC, NCCN included all drugs for non-CCRCC, and ESMO indicated the lack of standard therapy for non-CCRCC. The committee also discussed on the inclusion of temsirolimus, sunitinib and IFN-α for non-CCRCC. In view of the limited evidence on these drugs, all members who voted (100%) agreed to indicate 'no standard therapy', 'clinical trial preferred' and 'best supportive care' for non-CCRCC, much like the EAU guidelines. The members agreed that they would treat the mixed histology group as CCRCC as long as there is a predominant clear cell component in the histology, except with regard to the use of high-dose IL-2, where they would only use it on pure clear cell patients. The group emphasised that best supportive care should be added as an option in the local guideline for first-line mRCC management (Table 1).

2. Second-line Treatment for mRCC

Cytokine Refractory

Sorafenib

Sorafenib has been approved for the treatment of mRCC patients after failure of cytokine therapy.[28] The median PFS was 5.5 months in the sorafenib group and 2.8 months in the placebo group (HR = 0.44; 95% CI, 0.35 to 0.55; P <0.01). The first interim analysis of OS in May 2005 showed that sorafenib reduced the risk of death, as compared with placebo (HR = 0.72; 95% CI, 0.54 to 0.94; P = 0.02), although this benefit was not statistically significant according to the O'Brien-Fleming threshold. The comparison of sorafenib with best supportive care produced a base-case ICER of USD $139,182 per QALY gained for the combined group.[8]

Sorafenib was also found to be superior to temsirolimus in the INTORSECT study which enrolled patients who had failed VEGF TKI.[29]

Table 1. Singapore Cancer Network (SCAN) Guidelines for the Treatment of mRCC (Canadian Kidney Cancer Forum 2013 Guidelines)

First-line	Second-line	Third-line
CCRCC First Option: Clinical trials Good/Intermediate Risk: Sunitinib Bevacizumab + IFN-α Pazopanib High-dose IL-2 Active surveillance Poor Risk: Temsirolimus Sunitinib Pazopanib* Best supportive care	First Option: Clinical trials Cytokine Refractory: Sorafenib Pazopanib Axitinib Sunitinib Bevacizumab + IFN-α Best supportive care Prior VEGF Therapy: Everolimus Axitinib Anti-VEGF therapy not previously used Best supportive care Prior MTOR: Anti-VEGF targeted therapy Best supportive care	Anti-VEGF therapy not previously used† Best supportive care
Non-CCRCC No standard treatment available, patient should be treated in the framework of a clinical trial if available. Best supportive care is an option.		

CCRCC: Clear cell renal cell carcinoma; VEGF: Vascular endothelial growth factor
*No strong supporting evidence, to be used only as an alternative to sunitinib.
†Patient should be educated of the lack of data guiding third-line treatment for mRCC.

Axitinib

Axitinib has been approved for the treatment of mRCC patients after cytokine failure.[30] Median OS was 20.1 months (95% CI, 16.7 to 23.4) with axitinib and 19.2 months (95% CI, 17.5 to 22.3) with sorafenib (HR = 0.969; 95% CI, 0.800 to 1.174; one-sided $P = 0.3744$). Median investigator-assessed PFS was 8.3 months (95% CI, 6.7 to 9.2) with axitinib and 5.7 months (95% CI, 4.7 to 6.5) with sorafenib (HR = 0.656; 95% CI, 0.552 to 0.779; one-sided $P < 0.0001$).

Pazopanib

Pazopanib was approved for use in the second-line after cytokine failure based on the study by Sternberg et al, comparing it to placebo.[15]

Prior VEGF TKI

Axitinib

Axitinib has been approved for the treatment of mRCC patients after VEGF TKI failure.[30]

Everolimus

Everolimus has been approved for the treatment of mRCC patients after VEGF TKI failure.[31] The median PFS was 4.9 months (everolimus) versus 1.9 months (placebo) (HR = 0.33; $P < 0.001$) by independent central review and 5.5 months (everolimus) versus 1.9 months (placebo) (HR = 0.32; $P < 0.001$) by investigators' review.[32] The base-case ICER of everolimus versus best supportive care alone was reported as £89,547 per QALY gained.[10]

Recommendations for Second-line Treatment of mRCC

The workgroup voted 5 to 2 in support of the adaptation of the Canadian guideline (Supplementary Table 1), with the exclusion of tivozanib. The group suggested using the word anti-VEGF targeted therapy to make it clearer that drugs like 5-fluorouracil (5-FU) and tamoxifen should not be used. Besides the treatment options listed in the Canadian guidelines, it was also decided that best supportive care and clinical trials should be considered as part of the local treatment practice (Table 1).

3. Third-line Treatment of mRCC

No data is available. If the patient is physically fit to receive further treatment, there can be a discussion regarding the pros and cons of using a targeted therapy in the above list that has not been used before.

Recommendations for Third-line Treatment of mRCC

It was unanimously decided (100%) that the Canadian guideline can be adapted (Supplementary Table 1). In addition, the group agreed that it should be made clear to patients of the lack of data guiding treatment in third-line. Similar to that of first- and second-line, best supportive care will be listed as an option for third-line (Table 1).

Conflicts of Interest

Dr Kanesvaran reports receiving advisory board fees from Pfizer, GSK and Bayer and speaker bureau fees from Pfizer and GSK; Dr Ng, receiving advisory board fees from Bayer and Astra Zeneca; Dr Tan, receiving grant support from Pfizer, and holding the following pending patents: "A Multigene Assay for Prognosis and Drug Response Prediction in Clear-Cell Renal Cell Carcinoma Patients that Identifies Distinct Biological Subtypes", "Method for Predicting Clinical Toxicities and Outcomes in Patients Receiving Sunitinib Using Gene Polymorphisms", "Self-Assembled Micellar Nanocomplexes Comprising Polyethylene Glycol-Epigallocatechin-3-Gallate Conjugates and Anticancer Drugs", "Antibody Specific for parafibromin, a New Marker of Parathyroid Carcinoma", licensed to Santa Cruz Biotechnology, and "Method for Determining Mutation Status in Colorectal Cancer Patients Using Allele-Specific PCR", licensed to AIT Biotech; Dr Tan, Ms Tan, Dr Tay, Dr Toh and Dr Wong have nothing to disclose.

Workgroup Members

The Members of the SCAN Genitourinary Cancer Workgroup are Section Lead and Workgroup Chairperson: Ravindran Kanesvaran, MD, MRCP, FAMS, Department of Medical Oncology, National Cancer Centre Singapore, Singapore; Workgroup Members (Voting): Quan Sing Ng, MBBS, MD, MRCP, Department of Medical Oncology, National Cancer Centre Singapore, Singapore; Min-Han Tan, MBBS, FRCP, PhD, Department of Medical Oncology, National Cancer Centre Singapore, Singapore; Yew Oo Tan, MBBS, FAMS, Singapore Oncology Consultants, Singapore; Miah Hiang Tay, MBBS, MRCP, FAMS, Onco-Care Cancer Centre, Gleneagles Hospital, Singapore; Chee-Keong Toh, MBBS, MRCP, Department of Medical Oncology, National Cancer Centre Singapore, Singapore; Alvin Wong, MBBS, MRCP, Department of Haematology-Oncology, National University Health System, Singapore; Workgroup Members (Non-Voting): Hui Shan Tan, BSc, MPH, Department of Medical Oncology, National Cancer Centre Singapore, Singapore.

Reviewers

Invited reviewers were Ian F Tannock, MD, PhD, DSc, Princess Margaret Cancer Centre, University of Toronto, Canada; Brian Rini, MD, Taussig Cancer Institute, USA; Daniel Heng, MD, MPH, FRCPC, Department of Oncology, University of Calgary and Tom Baker Cancer Center, Canada. An additional invited reviewer chose to be anonymous.

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Supplementary Table 1. International Guidelines for the Treatment of mRCC

Guideline Title	NCCN Guidelines Version 2.2014 Kidney Cancer	Guidelines on Renal Cell Carcinoma (EAU)	Renal Cell Carcinoma: ESMO Clinical Practice Guidelines for Diagnosis, Treatment and Follow-up	Management of Advanced Kidney Cancer: Canadian Kidney Cancer Forum 2013 Consensus Update	NICE Guidance 1. Renal Cell Carcinoma–Sunitinib (TA169) 2. Renal Cell Carcinoma (TA178) 3. Renal Cell Carcinoma (First-line Metastatic)-Pazopanib (TA215) 4. Everolimus for the Second-line Treatment of Advanced Renal Cell Carcinoma (TA219)	Management of Kidney Cancer in Asia: Resource-Stratified Guidelines from the Asian Oncology Summit 2012
Date Released	2 December 2013	March 2013	7 October 2012	19 August 2013	1. March 2009, reviewed February 2011 2. August 2009, reviewed June 2011 3. February 2011, reviewed August 2013 4. April 2011	November 2012
Guideline Developer	National Cancer Comprehensive Network (NCCN), United States	European Association of Urology (EAU)	European Society for Medical Oncology (ESMO)	Kidney Cancer Research Network of Canada (KCRNC)	National Institute of Health and Clinical Excellence (NICE), United Kingdom	NUHS, NCCS, SGH, Gleneagles Singapore, Christian Medical College India, University of Indonesia
Description of Method of Guideline Validation	Statement of evidence and consensus of the authors regarding their views of currently accepted approaches to treatment. Validation method not specified.	Guidelines were developed through internal peer review. Appraisal of Guidelines for Research and Evaluation (AGREE) instrument was used to analyse and assess a range of specific attributes contributing to the validity of a specific clinical guideline. No formal external review prior to publication.	Recommendations developed from discussion at Consensus Conferences (CCs). Group decision-making that seeks the consensus of experts and the fulfilment of objectives.	Consensus statement was prepared on the basis of evidence from data published in peer-reviewed journals/texts/ abstracts from renowned international congresses, such as AUA, ASCO, ESMO and EAU.	Guidelines were developed through an open and transparent consultation process which allows individuals, patient groups, charities and industry to comment on recommendations.	Statement was formulated by a panel of urologists, medical oncologists, and clinical oncologists from Asian countries, at a consensus session on kidney cancer that was held as part of the 2012 Asian Oncology Summit in Singapore.
Target Population	Metastatic RCC	Metastatic RCC	Metastatic RCC	Metastatic RCC	Metastatic RCC	Metastatic RCC

AUA: American Urological Association; ASCO: American Society of Clinical Oncology; CCRCC: Clear cell renal cell carcinoma; mRCC: Metastatic renal cell carcinoma; NCCS: National Cancer Centre Singapore; NUHS: National University Hospital Singapore; PS: Performance status; RCC: Renal cell carcinoma; SGH: Singapore General Hospital; TKI: Tyrosine kinase inhibitor; VEGF: Vascular endothelial growth factor

Supplementary Table 1. International Guidelines for the Treatment of mRCC (Con't)

Guideline Title	NCCN Guidelines Version 2.2014 Kidney Cancer	Guidelines on Renal Cell Carcinoma (EAU)	Renal Cell Carcinoma: ESMO Clinical Practice Guidelines for Diagnosis, Treatment and Follow-up	Management of Advanced Kidney Cancer: Canadian Kidney Cancer Forum 2013 Consensus Update	NICE Guidance 1. Renal Cell Carcinoma–Sunitinib (TA169) 2. Renal Cell Carcinoma (TA178) 3. Renal Cell Carcinoma (First-line Metastatic)-Pazopanib (TA215) 4. Everolimus for the Second-line Treatment of Advanced Renal Cell Carcinoma (TA219)	Management of Kidney Cancer in Asia: Resource-Stratified Guidelines from the Asian Oncology Summit 2012
Systemic Therapy	First-line (CCRCC): - Clinical trial - Sunitinib - Temsirolimus* - Bevacizumab + IFN-α - Pazopanib - High dose IL-2† - Sorafenib - Best supportive care First-line (Non-CCRCC): - Clinical trial (preferred) - Temsirolimus* - Sorafenib - Sunitinib - Pazopanib - Axitinib - Everolimus - Bevacizumab - Erlotinib - Best supportive care	First-line (CCRCC, Good/Intermediate Risk): - Sunitinib - IFNa + bevacizumab - Pazopanib - IFN-α‡ - High-dose IL-2‡ First-line (CCRCC, Poor risk) - Temsirolimus First-line (Non-CCRCC): - No standard treatment available, patient should be treated in the framework of clinical trials	First-line (CCRCC, Good/Intermediate risk): - Sunitinib§ - Bevacizumab + IFN-α§ - Pazopanib§ - Cytokines (including high-dose IL2)‖ - Sorafenib‖ First-line (CCRCC, Poor Risk): - Temsirolimus§ - Sunitinib‖ - Sorafenib‖ First-line (Non-CCRCC) -No standard therapy -Temsirolimus‖ -Sunitinib‖ -Sorafenib‖	First Option: - Clinical trials First-line (Good/Intermediate Risk): - Sunitinib - Bevacizumab + IFN-α - Pazopanib - Tivozanib - High-dose IL-2¶ - Sorafenib¶ - Observation¶ First-line (Poor Risk): - Temsirolimus - Sunitinib¶	TA169: Sunitinib: - Recommended as first-line treatment option for advanced mRCC who are suitable for immunotherapy and have ECOG PS of 0 or 1 TA178: Bevacizumab, Sorafenib, Temsirolimus: - Not recommended as first-line treatment options for advanced mRCC Sorafenib, Sunitinib: - Not recommended as second-line treatment options for advanced mRCC TA215: Pazopanib: - Recommended as first-line treatment option for advanced RCC without prior cytokine	According to Resource Level: 1. Basic First-line: - Best supportive care Second-line: Nil 2. Limited First-line: - IFN-α - Targeted therapy with assistance programme - Clinical trials Second-line: - Clinical trials 3. Enhanced First-line: - Most cost-effective approved first-line therapy - Clinical trials Second-line: - Most cost-effective second-line therapy - Clinical trials
Member Votes				7 of 7 votes		
	Second- & Subsequent-line (CCRCC): - Clinical trial Second- & Subsequent-line (Cytokine Refractory, CCRCC): - Axitinib	Second-line (CCRCC, Cytokine Refractory): - Sorafenib - Axitinib - Pazopanib	Second-line (CCRCC, Cytokine Refractory): -Sorafenib# -Pazopanib# -Axitinib# -Sunitinib**	Second-line (Cytokine Refractory): - Sorafenib - Pazopanib - Tivozanib - Axitinib		

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	- Sorafenib - Sunitinib - Pazopanib - Temsirolimus - Bevacizumab Second- & Subsequent-line (Prior TKI Therapy, CCRCC): - Everolimus - Axitinib - Sorafenib - Sunitinib - Temsirolimus - Bevacizumab - Pazopanib Second- & Subsequent-line (Others): - IL-2 - Best supportive care Second- & Subsequent-line (Non-CCRCC): - No specific recommendations	Second-line (CCRCC, Prior TKI Therapy): - Axitinib - Sorafenib - Everolimus Second-line (Non-CCRCC): - No standard treatment available	Second-line (CCRCC, Prior TKI Therapy): -Everolimus[#] -Axitinib[#] -Sorafenib[**] Second-line (Non-CCRCC) -no standard therapy -clinical trial -Temsirolimus[**] -Sunitinib[**] -Sorafenib[**]	- Sunitinib[††] - Bevacizumab + IFN-α[††] Second-line (Prior VEGF Therapy): - Everolimus - Axitinib - Targeted therapy not previously used[††] Second (Prior MTOR): - VEGF TKI[††]	therapy and have ECOG PS of 0 or 1, and if the manufacturer provides 12.5% discount on the list price as agreed in the patient access scheme. TA219: Everolimus: - Not recommended for the second-line treatment of advanced RCC	4. Maximum First-line: - High-dose IL-2 in carefully selected patients - Any approved first-line therapy - Clinical trials Second-line: - Any approved second-line-therapy - Clinical trials
Member Votes				7 of 7 votes		
		Third-line (CCRCC Prior TKI Therapy): - Everolimus Third-line (Non-CCRCC): - No standard treatment available	Third-line (CCRCC, Prior 2 TKIs): - Everolimus[‡‡] Third-line (Non-CCRCC) -No standard therapy -Temsirolimus[§§] -Sunitinib[§§] -Sorafenib[§§]	Third-line (Any): - Targeted therapy not previously used[‖]		
Member Votes				7 of 7 votes		

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[*]for poor prognosis patients; [†]for excellent PS and normal organ function; [‡]in selected patients; [§]standard; [‖]option; [¶]Less than level 1 evidence; [#]standard; [**]option; [††]Less than level 1 evidence; [‡‡]standard; [§§]option; [‖‖]Less than level 1 evidence