

Pan-Asian adapted ESMO Clinical Practice Guidelines for the diagnosis, treatment and follow-up of patients with renal cell carcinoma.

Title: Pan-Asian adapted ESMO Clinical Practice Guidelines for the diagnosis, treatment and follow-up of patients with renal cell carcinoma.

Publication year: 2021

Journal: ESMO open

Authors: Division of Medical Oncology, National Cancer Centre Singapore, Singapore, Singapore. Electronic address: ravindran.kanesvaran@singhealth.com.sg.

Society: European Society for Medical Oncology

Origin country: International (Europe)

Target countries: Europe

DOI: 10.1016/j.esmoop.2021.100304

PMID: 34864348

Source: <https://pubmed.ncbi.nlm.nih.gov/34864348/>

pmc ESMO Open ESMO Open 3084 esmo 101690685 ESMO Open 2059-7029 Elsevier
PMC8645910 PMC8645910.1 8645910 8645910 34864348 10.1016/j.esmoop.2021.100304
S2059-7029(21)00266-0 100304 1 Special Article Pan-Asian adapted ESMO Clinical Practice
Guidelines for the diagnosis, treatment and follow-up of patients with renal cell carcinoma
Kanesvaran R. ravindran.kanesvaran@singhealth.com.sg 1 * Porta C. 2 Wong A. 3 Powles T. 4 Ng
Q.S. 1 Schmidinger M. 5 Ye D. 6 Malhotra H. 7 Miura Y. 8 Lee J.L. 9 Chong F.L.T. 10 Pu Y.-S. 11
Yen C.-C. 12 Saad M. 13 Lee H.J. 14 Kitamura H. 15 Bhattacharyya G.S. 16 † Curigliano G. 17
Poon E. 1 Choo S.P. 1 18 Peters S. 19 Lim E. 1 Yoshino T. 20 Pentheroudakis G. 21 1 Division of
Medical Oncology, National Cancer Centre Singapore, Singapore, Singapore 2 Department of
Biomedical Sciences and Human Oncology, University of Bari 'A. Moro' and Division of Medical
Oncology, A.O.U. Consorziale Policlinico di Bari, Bari, Italy 3 Department of
Haematology-Oncology, National University Cancer Institute, Singapore, Singapore 4 Barts Cancer
Institute, Queen Mary University, London, UK 5 Department of Urology I, and Comprehensive
Cancer Center, Medical University of Vienna, Vienna, Austria 6 Department of Urology, Fudan
University Shanghai Cancer Center, Shanghai, China 7 Department of Medical Oncology, Sri Ram
Cancer Center, Mahatma Gandhi Medical College Hospital, Mahatma Gandhi University of Medical
Sciences & Technology, Jaipur, India 8 Department of Medical Oncology, Toranomon Hospital,
Tokyo, Japan 9 Department of Oncology, Asan Medical Center, University of Ulsan College of
Medicine, Seoul, Korea 10 Department of Radiotherapy and Oncology, Sabah Women and
Children's Hospital, Kota Kinabalu, Sabah, Malaysia 11 Department of Urology, National Taiwan
University Hospital, Taipei, Taiwan 12 Division of Clinical Research, Department of Medical
Research and Division of Medical Oncology, Center for Immuno-oncology, Department of
Oncology, Taipei Veterans General Hospital and National Yang Ming Chiao Tung University School
of Medicine, Taipei, Taiwan 13 Department of Clinical Oncology, University of Malaya Medical
Centre, Faculty of Medicine, Universiti Malaya, Kuala Lumpur, Malaysia 14 Department of Medical
Oncology, Chungnam National University Hospital, Chungnam National University College of
Medicine, Daejeon, Korea 15 Department of Urology, Faculty of Medicine, University of Toyama,
Toyama, Japan 16 Salt Lake City Medical Center, Kolkata, India 17 Istituto Europeo di Oncologia,
IRCCS and University of Milano, Milan, Italy 18 Medical Oncology, Curie Oncology, Singapore,
Singapore 19 Oncology Department, Lausanne University Hospital (CHUV), Lausanne, Switzerland
20 Department of Gastroenterology and Gastrointestinal Oncology, National Cancer Center
Hospital East, Kashiwa, Japan 21 ESMO, Lugano, Switzerland * Correspondence to: Associate
Prof. Ravindran Kanesvaran, Division of Medical Oncology, National Cancer Centre Singapore, 11
Hospital Crescent, Singapore 169610, Singapore. Tel: +6564368000; Fax: +6562272759
ravindran.kanesvaran@singhealth.com.sg † Sadly, we report that the eminent Indian medical
oncologist Professor Gouri Shankar Bhattacharyya, who contributed to the pre-meeting survey for

these guidelines, succumbed to Covid-19 only a few days before the virtual face-to-face meeting. We acknowledge, along with many others, his contribution to medical oncology not only in India but internationally, and also his contribution to the Pan-Asian adaptation of the present guidelines and previously to the Pan-Asian adaptation of the ESMO hepatocellular carcinoma guidelines.

12 2021 01 12 2021 6 6 391737 100304 01 12 2021 15 12 2021 08 05 2024 © 2021 The Authors 2021 <https://creativecommons.org/licenses/by-nc-nd/4.0/> This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>). ESMO Clinical Practice Guidelines: adapting and adopting new approaches for development, implementation and audit 7 1 10 1 2022 100344 ESMO Open 10.1016/j.esmoop.2021.100344 PMC8760392 35026722 The most recent version of the European Society for Medical Oncology (ESMO) Clinical Practice Guidelines for the diagnosis, treatment and follow-up of renal cell carcinoma was published in 2019 with an update planned for 2021. It was therefore decided by both the ESMO and the Singapore Society of Oncology (SSO) to convene a special, virtual guidelines meeting in May 2021 to adapt the ESMO 2019 guidelines to take into account the ethnic differences associated with the treatment of renal cell carcinomas in Asian patients. These guidelines represent the consensus opinions reached by experts in the treatment of patients with renal cell carcinoma representing the oncological societies of China (CSCO), India (ISMPO), Japan (JSMO), Korea (KSMO), Malaysia (MOS), Singapore (SSO) and Taiwan (TOS). The voting was based on scientific evidence and was independent of the current treatment practices and drug access restrictions in the different Asian countries. The latter were discussed when appropriate.

- This article provides ESMO expert recommendations adapted for the treatment of renal cell carcinomas in Asian patients.

The aim was to provide guidance for the optimisation of the management of such patients across Asia.

The availability and applicability of certain procedures as they relate to certain of the recommendations are discussed.

In 2018, an estimated 18.1 million new cases of cancer were diagnosed and 9.6 million cancer-related deaths recorded, worldwide. 1 Of these, kidney cancer accounted for 2.2% (403 262) of new cases of cancer across both sexes, and 1.8% (175 098) of cancer deaths. 1 Significantly, almost two-thirds (254 500) of new kidney cancer cases are diagnosed in men. Approximately 70% of kidney cancers are clear cell renal cell carcinomas (ccRCC), 2 which typically metastasise to the lungs, liver and bone. 3 Other subtypes with an incidence $\geq 5\%$ are papillary RCC and chromophobe RCC, with each of the remaining subtypes accounting for $\leq 1\%$ of the total incidence. 4 , 5 Because of the predominance of ccRCC, however, kidney cancer can be broadly classified into either ccRCC or non-ccRCC (nccRCC).

The highest incidence rates of kidney cancer/RCC are found in Northern and Eastern Europe, North America, Australia and New Zealand and the lowest in Asia. 6 The incidence of kidney cancer has increased, however, and continues to increase in many Asian countries. 7 , 8 , 9 A study of the incidence and mortality rates for kidney cancer in Asia reported a total of 121 099 kidney cancer cases in Asian countries in 2012, 7 with the highest incidences of new cases being in China (66 466 new cases), Japan (16 830 new cases) and India (9658 new cases). South Korea, Japan and Singapore were among the top five Asian countries with the highest standardised incidence rates at 8/100 000, 5.3/100 000 and 5.2/100 000, respectively. A positive correlation was also demonstrated between the human development index and age-specific incidence and age-specific mortality rates for kidney cancer. 7 Risk factors include older age, smoking, obesity, diet and alcohol, hypertension, occupational exposure, chronic kidney disease and renal replacement therapy, and the regular use of non-aspirin nonsteroidal anti-inflammatory drugs. 10 , 11 Approximately 2%-3% of RCCs are hereditary, with the most common form being associated with von Hippel-Lindau syndrome. 12

Guidelines for the screening, treatment and management of patients with kidney cancer/RCC in Asia have been published previously, 13 , 14 , 15 , 16 , 17 , 18 and are important for the standardisation of both screening and treatment approaches with the aim of optimising clinical outcomes. The European Society for Medical Oncology (ESMO) Clinical Practice Guidelines for the diagnosis, treatment and follow-up of patients with RCC have recently been published (ESMO Clinical Practice Guidelines) 12 and a decision was taken by the ESMO and the Singapore Society of Oncology (SSO) that these guidelines, 12 and the associated updates to these guidelines, 19 , 20 should be adapted for patients of Asian ethnicity. Consequently, representatives of SSO, ESMO, the Chinese Society of Clinical Oncology (CSCO), the Indian Society of Medical and Paediatric Oncology (ISMPO), the Japanese Society of Medical Oncology (JSMO), the Korean Society of Medical Oncology (KSMO), the Malaysian Oncological Society (MOS) and the Taiwan Oncology Society (TOS) convened for a virtual, 'face-to-face' working meeting on 15 May 2021 to adapt the recent ESMO Clinical Practice Guidelines 12 and associated e-updates 19 , 20 for use in the management of Asian patients with RCC. This manuscript summarises the Pan-Asian adapted guidelines developed at the meeting accompanied by the level of evidence (LoE), grade of recommendation and percentage consensus reached for each recommendation.

This Pan-Asian adaptation of the current ESMO Clinical Practice Guidelines and associated e-updates 12 , 19 , 20 was prepared in accordance with the principles of ESMO standard operating procedures (<http://www.esmo.org/Guidelines/ESMO-Guidelines-Methodology>) and was an SSO-ESMO initiative endorsed by CSCO, ISMPO, JSMO, KSMO, MOS and TOS.

An international panel of experts was selected from the SSO (n = 6), the ESMO (n = 7) and two experts from each of the oncological societies of India (ISMPO), Japan (JSMO), Korea (KSMO), Malaysia (MOS) and Taiwan (TOS), and one from the oncological society of China (CSCO). Only two of the six expert members from the SSO (AW and QSN) were allowed to vote on the recommendations together with the experts from each of the six other Asian oncology societies (n = 13). Of the 13 voting experts 3 were urologists [DY (CSCO), Y-SP (TOS) and HK (JSMO)] and the remainder oncologists.

A modified Delphi process was used to review, accept or adapt each of the individual recommendations in the latest ESMO Clinical Practice Guidelines. 12 The 13 Asian experts were asked to vote YES or NO (one vote per society) on the 'acceptability' (agreement with the scientific content of the recommendation) and 'applicability' (availability, reimbursement and practical challenges) of each of the ESMO recommendations in a pre-meeting survey (see Supplementary Methodology , available at <https://doi.org/10.1016/j.esmoop.2021.100304>). For recommendations, where a consensus was not reached, the Asian experts were invited to modify the wording of the recommendation(s) at the 'face-to-face' virtual meeting using rounds of voting in order to determine the definitive acceptance or rejection of an adapted recommendation and discuss the applicability challenges. The 'Infectious Diseases Society of America-United States Public Health Service Grading System' (Supplementary Table S1 , available at <https://doi.org/10.1016/j.esmoop.2021.100304>) 21 was used to define the LoE and strength (grade) of each recommendation. Any modifications to the initial recommendations were highlighted in bold text in a summary table of the final Asian recommendations and in the main text, if and as applicable. A consensus was considered to have been achieved when $\geq 80\%$ of experts voted that a recommendation was acceptable.

In the initial pre-meeting survey, the 13 Asian experts reported on the 'acceptability' and 'applicability' of the 37 recommendations for the diagnosis, treatment and follow-up of patients with RCC from the 2019 ESMO Clinical Practice Guidelines and associated updates. 12 , 19 , 20 These recommendations were made in the five categories listed below: • Diagnosis and pathology/molecular biology (Recommendations 1a-d)

Staging and risk assessment (Recommendation 2)

Management of local/locoregional disease (Recommendations 3a-g)

Management of advanced/metastatic disease (Recommendations 4a-u)

Follow-up, long-term implications and survivorship (Recommendations 5a-c)

A lack of agreement in the pre-meeting survey was established for 'recommendations 1a, 3f, and 4a, b and g' (with no consensus for 'acceptability') and 'recommendations 1a, 3c-e, and 4a-c, f-h, j-l, and n-p' (with no consensus for 'applicability'), leading to their discussion during the 'face-to-face' meeting (Supplementary Tables S2 and S3 , available at <https://doi.org/10.1016/j.esmoop.2021.100304>).

In addition, due to a flurry of new publications, 22 , 23 , 24 , 25 , 26 14 new recommendations from an ongoing e-update of the ESMO guidelines relating to the systemic therapy options for the treatment of advanced/metastatic disease 27 were added to the meeting agenda for discussion and potential inclusion immediately before the virtual 'face-to-face' meeting (Supplementary Table S4 , available at <https://doi.org/10.1016/j.esmoop.2021.100304>) and voted on during the virtual meeting.

More than 50% of RCCs are detected incidentally. In recent years, however, the use of non-invasive radiological techniques, such as ultrasonography (US) and computed tomography (CT), has facilitated the more frequent detection of small, early-stage RCCs, which are potentially curable. 12 Magnetic resonance imaging may provide additional information on the extent of disease but is not recommended for routine clinical practice.

Suspicion of RCC should result in the initiation of laboratory tests ('recommendation 1a' below), some of which are prognostic for survival and are used for risk assessment. 12 A core biopsy provides histopathological confirmation of malignancy, and is recommended before both treatment with ablative therapies [III, B] and, in the case of patients with metastatic disease, the initiation of systemic therapy [III, B]. 28 , 29 The Pan-Asian panel of experts agreed with and 'accepted' completely (100% consensus) the ESMO recommendations on diagnosis pathology/molecular biology 'recommendations 1b–d' below and Table 1 . Some reservations were expressed in terms of both the 'acceptability' and 'applicability' of 'recommendation 1a', however, and the type of laboratory tests carried out, in the pre-meeting survey (Supplementary Tables S2 and S3 , available at <https://doi.org/10.1016/j.esmoop.2021.100304>). As a consequence, the text of 'recommendation 1a' below was modified slightly (see bold text) to clarify which tests are considered to be mandatory, and 100% consensus achieved in terms of both 'acceptably' and 'applicability' (Table 1). 1a. Laboratory examinations of serum creatinine, haemoglobin, differential leukocyte and platelet counts, and serum-corrected calcium tests should be carried out to confirm a suspicion of RCC (full blood counts and renal profile tests are essential, the remainder of the tests may be carried out to facilitate the diagnosis/prognosis of RCC) [IV, B, consensus = 100%].

For accurate staging, US and contrast-enhanced chest, abdominal and pelvic CT scans are recommended [III, A].

A renal tumour core biopsy is recommended 28 , 29 before treatment with ablative therapies and in patients with metastatic disease before starting systemic treatment [III, B].

Pathology should be assessed using the 2016 World Health Organization histological classification of renal tumours and ISUP grading. 30

ccRCC, clear cell renal cell carcinoma; CT, computed tomography; EMA, European Medicines Agency; ESMO-MCBS, European Society for Medical Oncology-Magnitude of Clinical Benefit Scale; FDA, Food and Drug Administration; Gy, gray; IMDC, International Metastatic RCC Database Consortium; MET, mesenchymal-epithelial transition; mRCC, metastatic renal cell carcinoma; PD-1, programmed cell death protein 1; PD-L1, programmed death-ligand 1; PS,

performance status; RCC, renal cell carcinoma; RCT, randomised controlled trial; RT, radiotherapy; TKIs, tyrosine kinase inhibitors; TNM, tumour–node–metastasis; UICC, Union for International Cancer Control; US, ultrasound; VEGFR, vascular endothelial growth factor receptor; WHO, World Health Organization.

The Pan-Asian panel of experts agreed completely (100% consensus) with the ESMO recommendations on diagnosis, 'recommendation 2' below (Table 1), after the pre-meeting survey, from both a scientific ('acceptability') and 'applicability' point of view. 2. The Union for International Cancer Control (UICC) TNM (tumour–node–metastasis) 8 staging system should be used. 31

Management of localised RCC can involve partial or radical nephrectomy (RN), ablation or active surveillance, and the Pan-Asian panel of experts agreed with and accepted completely (100% consensus) the ESMO recommendations 3a–c below and Table 1 on the management of local and locoregional disease without change. 3a. For organ confined T1 tumours <7 cm, partial nephrectomy (PN) is recommended [I, A]. Laparoscopic RN is recommended if PN is not feasible [I, A].

In patients with compromised renal function, solitary or bilateral tumours, PN is also recommended with no tumour size limitation.

Radiofrequency ablation (RFA), microwave ablation or cryoablation (CA) are options in patients with small cortical tumours (≤ 3 cm), frail patients, high surgical risk, solitary kidney, compromised renal function and hereditary RCC or bilateral tumours [III, B].

The Asian experts, however, did not consider 'recommendation 3d' acceptable in the pre-meeting survey (Supplementary Table S2 , available at <https://doi.org/10.1016/j.esmoop.2021.100304>). Renal biopsy is sometimes omitted in some Asian countries especially if imaging techniques, such as dynamic contrast-enhanced CT, show features typical of clear cell carcinoma, and the patients are scheduled for nephrectomy (but not RFA or CA). Renal biopsy may be considered in selected patients, for example in young patients, to rule out other renal histopathological subtypes. As a consequence, the text of the 'recommendation 3d' was amended with the changes highlighted in bold text, to read as follows: 3d. When nephrectomy is not contemplated or possible, a renal biopsy is recommended to confirm malignancy and histopathological subtype [V, C; consensus = 100%, Table 1].

The Asian experts agreed with and accepted completely (100% consensus) the ESMO 'recommendation 3e' below in terms of 'acceptability' and 'applicability', without major change (Table 1). 3e. Active surveillance may be selected for elderly patients with significant comorbidities or those with short life expectancy and solid renal tumours <40 mm [II, B]; renal biopsy is recommended to select these patients.

Initially, following the pre-meeting survey, there was some discussion around the fact that PN might be an option if technically feasible, but the Asian experts agreed after discussion to accept completely 'recommendation 3f' below without change (Table 1). 3f. For T2 tumours >7 cm, laparoscopic RN is the preferred option [consensus = 100%].

The Asian experts also agreed with and accepted completely (100% consensus) the ESMO 'recommendation 3g' below in terms of 'acceptability' and 'applicability', without change (Table 1). 3g. For T3 and T4 tumours (locally advanced), open RN is the standard of care, although a laparoscopic approach can be considered.

Despite the role of surgery and local therapy, ~30% of patients with localised RCC develop metastases with the highest risk of ccRCC-related death seen in younger and high-risk patients. 32 Although PN and RN are typically used for the management of localised disease, cytoreductive

nephrectomy (CN) is an appropriate treatment modality for selected patients with metastatic disease.

The Asian experts considered the initial ESMO 'recommendation 4a' (Supplementary Table S2 , available at <https://doi.org/10.1016/j.esmoop.2021.100304>) controversial in view of the fact that the role of CN itself is controversial. 33 , 34 , 35 The benefit of CN for overall survival (OS) is unclear in patients with synchronous metastatic RCC (mRCC) in the era of targeted and immune-based therapies. In some Asian centres, CN is only carried out if the patient can tolerate the procedure, and the tumour volume of the primary is greater than that of the metastatic sites, or if a reasonable level of debulking and symptom relief can be achieved. CN together with metastasectomy for single metastases or oligometastases may improve survival [III, B]. Data from a large meta-analysis (n = 33 196 patients) 36 also suggests that clinical practice mostly originates from nephrectomised patients. Thus, the wording of 'recommendation 4a' was modified, with the changes highlighted in bold text, to read as follows: 4a. CN is recommended in patients with good PS, 37 low metastatic burden and/or symptomatic primary tumours either as up-front surgery or delayed nephrectomy 38 , 39 [III, B; consensus = 100%].

The original 'recommendation 4b' (Supplementary Table S2 , available at <https://doi.org/10.1016/j.esmoop.2021.100304>) was deleted as most patients with an unresectable primary tumour do not receive radiotherapy (RT). RT is only used for metastases to provide pain relief or in other palliative settings.

The Asian experts also agreed with and accepted completely (100% consensus) the original ESMO 'recommendations 4c-f' (now 'recommendations 4b-e') below in terms of 'acceptability' and 'applicability', without change (Table 1). At the 'face-to-face' meeting, however, there was much discussion about the meaning of 'good prognosis' in the original 'recommendation 4e' below ('recommendation 4f' Supplementary Table S2 , available at <https://doi.org/10.1016/j.esmoop.2021.100304>). As a consequence, the wording of 'recommendation 4e' was revised, with the changes highlighted in bold text (below and Table 1). 4b. Image-guided RT techniques such as volumetric-modulated arc therapy (VMAT) or stereotactic body RT (SBRT) are needed to enable the delivery of a high dose [IV, B].

RT is an effective treatment for palliation of local and symptomatic mRCC disease or to prevent the progression of metastatic disease in critical sites such as the bones or brain 40 , 41 [III, A].

For mRCC patients with brain metastases, the use of corticosteroids can provide temporary relief of cerebral symptoms. Whole-brain RT (WBRT) between 20 and 30 Gy in 4-10 fractions is recommended for effective symptom control 42 [II, B].

For mRCC patients with a limited number of brain metastasis, surgery and/or stereotactic radiosurgery with or without WBRT should be considered 43 , 44 [II, A; consensus = 100%].

The past 16 years has seen a number of targeted therapeutic agents approved for the treatment of RCC. These include agents that more or less selectively target the vascular endothelial growth factor (VEGF)/VEGF receptor (VEGFR) signalling axis, the mammalian target of rapamycin (mTOR) inhibitors everolimus and temsirolimus, as well as the programmed cell death protein 1 (PD-1)/programmed death-ligand 1 (PD-L1) and cytotoxic T lymphocyte-associated antigen 4 (CTLA4) pathway immune checkpoint inhibitors that elicit the antitumour immune response. 45 , 46 , 47 , 48 , 49 , 50 The applicability of these agents to the treatment of Asian patients with mRCC has also been investigated and confirmed. 9 , 51 , 52 , 53 , 54 , 55 , 56 Currently, doublet combinations of these agents and single-agent therapy form the backbone of the first- and second-line systemic therapy approaches, respectively, for patients with RCC (Table 1 and Figure 1). Single-agent therapy with VEGF pathway tyrosine kinase inhibitors (TKIs) is a first-line treatment option in patients where immune therapy is contraindicated or not available. Figure 1 Systemic first-line and subsequent line treatment of ccRCC.

ccRCC, clear cell renal cell carcinoma; EMA, European Medicines Agency; ESMO-MCBS, European Society for Medical Oncology-Magnitude of Clinical Benefit Scale.

a ESMO-MCBS scores for new therapies/indications approved by the EMA since 1 January 2016. The scores have been calculated by the ESMO-MCBS Working Group and validated by the ESMO Guidelines Committee.

b Where recommended treatment not available or contraindicated.

The Asian experts also agreed with and accepted completely (100% consensus) the original ESMO 'recommendations 4h-k' (now 'recommendations 4f and g' below, with the original recommendation 4j incorporated into the new recommendation 4i) (Supplementary Table S2 , available at <https://doi.org/10.1016/j.esmoop.2021.100304>) in terms of 'acceptability' and 'applicability', without change. The Asian experts also reviewed and voted on seven new recommendations and one confirmatory recommendation for first-line systemic therapy in patients with ccRCC (Supplementary Table S4 , available at <https://doi.org/10.1016/j.esmoop.2021.100304>), introduced immediately before the 'face-to-face' virtual meeting, and taken from the latest ESMO guidelines update for the treatment of RCC, 27 pre-publication. The list of recommendations below for the first-line treatment of RCC 'recommendations 4f-m' represents an amalgamation of the two. The original ESMO 'recommendation 4g' (Supplementary Table S2 , available at <https://doi.org/10.1016/j.esmoop.2021.100304>) was deleted as being out of date.

The Asian experts agreed with and accepted completely (100% consensus) the updated list of 'recommendations 4f-m' below and Table 1 in terms of both 'acceptability' and 'applicability', with minor modifications indicated in bold text, and the recognition that due to a lack of comparative trials, there is no preferred VEGFR/PD-1 first-line treatment combination, 'recommendations 4f-h'. 4f. The combination of axitinib and pembrolizumab (AP) is recommended as a first-line therapeutic option for patients with advanced disease, irrespective of International Metastatic RCC Database Consortium (IMDC) prognostic subgroup and PD-L1 biomarker status [I, A; ESMO-Magnitude of Clinical Benefit Score (MCBS) v1.1 score: 4].

The combination of cabozantinib and nivolumab is recommended as a first-line therapeutic option for advanced disease irrespective of IMDC prognostic subgroup and PD-L1 biomarker status [I, A; ESMO-MCBS v1.1 score: 4] (e-Update 30 Nov20). 20

Lenvatinib and pembrolizumab join the other VEGFR/PD-1-targeting combinations (AP and cabozantinib and nivolumab) to be recommended as a first-line treatment option for patients with advanced ccRCC, irrespective of the IMDC prognostic subgroup and PD-L1 biomarker status [I, A; ESMO-MCBS v1.1 score: 4]. 22 , 23 , 57 The combination of ipilimumab and nivolumab (IN) should be considered as a first-line option in patients with IMDC intermediate- and poor-risk disease [I, A, ESMO-MCBS v1.1 score: 4] (e-Update 7 Feb20, and Figure 1). 47 , 48

Sunitinib [I, A], 58 pazopanib [I, A] 59 and tivozanib [II, B] 60 are alternatives to immune checkpoint inhibitor-based first-line combinations when immune therapy is contraindicated or not available. Cabozantinib is also an alternative for the treatment of IMDC intermediate- [II, A; ESMO-MCBS v1.1 score: 3] and poor-risk disease in those patients who cannot receive first-line immune checkpoint inhibitor-based therapy [II, B; ESMO-MCBS v1.1 score: 3]. 61

Sunitinib or pazopanib are potential alternatives to immune checkpoint inhibitor-based combination therapy in patients with IMDC favourable-risk disease due to a lack of clear superiority for immune checkpoint inhibitor-based combinations over sunitinib in this subgroup of patients in randomised, controlled trials (RCTs). Pazopanib was found to be non-inferior to sunitinib in the COMPARZ study 59 [III, C; ESMO-MCBS v1.1 score: 4].

Active surveillance is an alternative approach in a small subset of patients. This requires careful consideration in patients with good prognostic features [III, B]. 62

Axitinib and avelumab, 46 and bevacizumab and atezolizumab, 63 are not yet associated with an OS advantage and are therefore not recommended [I, C].

Cessation of immune checkpoint inhibitors can be considered after 2 years of therapy in selected patients with good disease control. [IV, B].

There are limited data for treatment after progression or intolerance on AP or IN, and VEGFR TKIs are the recommended treatment for these patients [III, B].

The Asian experts agreed with and accepted completely (100% consensus) the original ESMO recommendations 4l, n and p (Supplementary Tables S2 and S3 , available at <https://doi.org/10.1016/j.esmoop.2021.100304>), now 'recommendations 4n-p' below, in terms of 'acceptability' and 'applicability', without change (Table 1). At the 'face-to-face' meeting, however, there was much discussion about 'recommendation 4o' due to the limited available information about toxicity and efficacy, and the feeling that there was no reason to favour one TKI over another. The feeling amongst the experts was that the combination of lenvatinib and everolimus was also a good candidate for second-line therapy after AP or cabozantinib plus nivolumab. The wording of 'recommendation 4o' below was therefore revised to reflect this (see bold text below and Table 1).

'Recommendations 4q and r' taken from the latest update to the ESMO guidelines (Powles 2021 e-update in preparation) (Supplementary Table S4 , available at <https://doi.org/10.1016/j.esmoop.2021.100304>) were also accepted with 100% consensus. 4n. For second-line treatment, following TKIs, nivolumab [I, A; ESMO-MCBS v1.1 score: 5] or cabozantinib is recommended [I, A; ESMO-MCBS v1.1 score: 3].

The combination of lenvatinib and everolimus is FDA- and EMA-approved after TKI failure [II, B; ESMO-MCBS v1.1 score: 4] and could be considered following progression after first-line TKI monotherapy or a TKI in combination with an immune checkpoint inhibitor [IV, C].

In patients already treated with two lines of TKI therapy and whose disease has progressed , either nivolumab [I, A; ESMO-MCBS v1.1 score: 5] or cabozantinib [I, A; ESMO-MCBS v1.1 score: 3] may be considered.

Sequencing VEGFR TKI therapy after PD-1-based first-line therapy is associated with modest response rates. 64 , 65 , 66 Thus, patients should receive a VEGFR-targeted agent that they have not received previously [III, A].

RCT data to support continued immune checkpoint inhibition after established progression is lacking, and hence it is not recommended.

Clinical data for the medical treatment of the rarer non-clear cell subtypes of RCC are relatively limited 67 , 68 , 69 and there are no available data for post first-line therapy except for papillary carcinoma. The systemic therapy options for metastatic nccRCC include targeted therapies, such as TKIs, immune checkpoint inhibitors, and, for specific rare subtypes (mainly collecting duct and medullary carcinomas), cytotoxic chemotherapy 70 , 71 (Figure 2). Figure 2 Systemic first-line treatment of non-ccRCC.

MET, mesenchymal-epithelial transition gene; non-ccRCC, non-clear cell renal cell carcinoma.

In the open-label randomised phase II SWOG 1500 study (NCT02761057), 72 conducted in the USA and Canada, eligible patients with metastatic papillary RCC who had received up to one previous therapy [excluding VEGF-directed and mesenchymal-epithelial transition (MET)-directed

agents], were randomly assigned to receive sunitinib, cabozantinib, crizotinib or savolitinib.

Cabozantinib reduced the risk of disease progression or death by 40% when compared with sunitinib, with a median progression-free survival (PFS) in the cabozantinib group of 9.0 months, compared with 5.6 months, for the sunitinib group (hazard ratio 0.60, 0.37-0.97, $P = 0.019$). The response rate was also superior for cabozantinib at 23% versus 4% for sunitinib ($P = 0.010$). Savolitinib and crizotinib did not improve PFS compared with sunitinib, and those arms of the study were terminated prematurely. Grade 3 or 4 adverse events occurred in 31 (69%) of 45 patients receiving sunitinib, and 32 (74%) of 43 patients receiving cabozantinib. 72 There was one grade 5 thromboembolic event recorded in the cabozantinib group. Thus, cabozantinib looks to be a promising new first-line option for papillary RCC. 70 Data on checkpoint inhibitors in this setting have also been reported. 25 In the absence of definitive data, systemic therapy that has not been given previously should be given second line (Figure 2).

The Asian experts agreed with and accepted completely (100% consensus) the ESMO 'recommendations 4s, t, u and v' below (Supplementary Table S4 , available at <https://doi.org/10.1016/j.esmoop.2021.100304>) in terms of 'acceptability' and 'applicability', without change (Table 1). 4s. Cabozantinib is the preferred first-line agent in patients with advanced papillary RCC who have not undergone additional molecular testing 72 [II, B].

Alternative options include sunitinib [II, B] and pembrolizumab [III, B], while in MET -driven tumours, savolitinib can be considered (where available) 26 , 73 [III, C].

Immune checkpoint inhibitor-based therapy is particularly active in sarcomatoid renal tumours and should be recommended ahead of single-agent VEGFR-targeted therapy [II, A]. 22 , 23 , 57 , 74 , 75

Second-line therapy should focus on those first-line agents that have not been used previously [IV, C].

The Asian experts also agreed with and accepted completely (100% consensus) the original ESMO 'recommendations 5a- c' below, in terms of 'acceptability' and 'applicability', with a slight modification of 'recommendation 5a' for the sake of clarification. 5a. Follow-up for high-risk patients includes CT scans of thorax and abdomen every 3-6 months for the first 2 years, although the risk of late or even very late relapses should be taken into account ; an annual CT scan is recommended for low-risk patients.

For mRCC patients receiving systemic therapy, 2- to 4-month follow-up with a CT scan is advised.

RECIST is the most frequently used method to assess drug efficacy.

The drug and treatment availability for each of the seven Asian countries is summarised in Table 2 and the ESMO-MCBSs for the different systemic therapy options and new therapy combinations for the treatment of RCC are presented in Table 3 . Resource limitations are the most important barrier to offering optimal diagnosis and treatment to patients with RCC across the different Asian countries. Table 2 Summary of applicability (availability) of drugs, equipment and testing according to Asian country

CA, cryoablation; CSCO, Chinese Society of Clinical Oncology; ISMPO, Indian Society of Medical and Paediatric Oncology; MWA, microwave ablation; JSMO, Japanese Society of Medical Oncology; KSMO, Korean Society of Medical Oncology; RFA, radiofrequency ablation; RN, radical nephrectomy; SBRT, stereotactic body radiotherapy; SRS, stereotactic radiosurgery; SSO, Singapore Society of Oncology; TOS, Taiwan Oncology Society; VMAT, volumetric-modulated arc therapy.

ESMO-MCBS table for new therapies/indications in renal cell carcinoma a

CI, confidence interval; ESMO-MCBS, European Society for Molecular Oncology-Magnitude of Clinical Benefit Scale; HR, hazard ratio; ITT, intention-to-treat; mTOR, mammalian target of rapamycin; NS, not significant; OS, overall survival; PFS, progression-free survival; QoL, quality of life; Q-TWIST, quality-adjusted time without symptoms and toxicity; RCC, renal cell carcinoma; TKIs, tyrosine kinase inhibitors; UL, upper limit; VEGF, vascular endothelial growth factor; VEGFR, vascular endothelial growth factor receptor.

European Medicines Agency (EMA) approvals from January 2016 and Food and Drug Administration (FDA) approvals since January 2020.

ESMO-MCBS version 1.1. 87 The scores have been calculated by the ESMO-MCBS Working Group and validated by the ESMO Guidelines Committee.

More than 30% of control arm patients never received subsequent immunotherapy, suboptimal post progression treatment may exaggerate OS benefit. 88

Calculated estimate of gain based on point estimate HR 0.68.

QoL evaluated as an exploratory endpoint (as distinct from primary or secondary endpoint) is not eligible for ESMO-MCBS grading.

Form 2a cannot be applied since median OS was not reached in the control arm, consequently, score derived from 2b criteria with an upgrade for early stopping based on OS advantage detected at interim analysis.

The results of the voting by the Asian experts both before and after the 'face-to-face' meeting showed high concordance (Supplementary Tables S2 and S3 , available at <https://doi.org/10.1016/j.esmoop.2021.100304>) with the ESMO recommendations for the treatment of patients with RCC. Following the 'face-to-face' discussions, the revisions made to the wording of 'recommendations 1a, 3d and 4a', the deletion of the original 'recommendation 4g', the incorporation of the original 'recommendation 4j' into the new 'recommendation 4i' and the introduction of the new 'recommendations 4h, i, j and r–v' (above and Table 1) resulted in a 100% consensus in terms of 'acceptability' being achieved for all the recommendations listed in Table 1 .

Thus, the recommendations listed in Table 1 can be considered to constitute the consensus clinical practice guidelines for the treatment of patients with RCC in Asia. As mentioned previously, the acceptance of each recommendation by each of the Asian experts was based on the available scientific evidence and was independent of the approval and reimbursement status of certain drugs in their individual countries. A summary of the availability of the recommended treatment modalities and recommended drugs, as of May 2021, is presented for each participating Asian country in Table 2 and will obviously impact on some of the disease and patient management strategies that can be adopted by certain countries.

Bray F. Ferlay J. Soerjomataram I. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries *CA Cancer J Clin* 68 2018 394 424 30207593 10.3322/caac.21492 2 Gansler T. Fedewa S. Amin M.B. Trends in reporting histological subtyping of renal cell carcinoma: association with cancer center type *Hum Pathol* 74 2018 99 108 29339177 10.1016/j.humpath.2018.01.010 3 Chevrier S. Levine J.H. Zanotelli V.R.T. An immune atlas of clear cell renal cell carcinoma *Cell* 169 2017 736 749.e718 28475899 10.1016/j.cell.2017.04.016 PMC5422211 4 Hsieh J.J. Purdue M.P. Signoretti S. Renal cell carcinoma *Nat Rev Dis Primers* 3 2017 17009 28276433 10.1038/nrdp.2017.9 PMC5936048 5 Shuch B. Amin A. Armstrong A.J. Understanding pathologic variants of renal cell carcinoma: distilling therapeutic opportunities from biologic complexity *Eur Urol* 67 2015 85 97 24857407

10.1016/j.eururo.2014.04.029 6 Patel A.R. Prasad S.M. Shih Y.C. The association of the human development index with global kidney cancer incidence and mortality J Urol 187 2012 1978 1983 22498216 10.1016/j.juro.2012.01.121 7 Arabsalmani M. Mohammadian-Hafshejani A. Ghoncheh M. Incidence and mortality of kidney cancers, and human development index in Asia; a matter of concern J Nephropathol 6 2017 30 42 28042551 10.15171/jnp.2017.06 PMC5106880 8 Chow W.H. Dong L.M. Devesa S.S. Epidemiology and risk factors for kidney cancer Nat Rev Urol 7 2010 245 257 20448658 10.1038/nrurol.2010.46 PMC3012455 9 Koo K.C. Lee K.S. Chung B.H. Urologic cancers in Korea Jpn J Clin Oncol 45 2015 805 811 26117494 10.1093/jjco/hyv096 10 Choueiri T.K. Je Y. Cho E. Analgesic use and the risk of kidney cancer: a meta-analysis of epidemiologic studies Int J Cancer 134 2014 384 396 23400756 10.1002/ijc.28093 PMC3815746 11 Padala S.A. Barsouk A. Thandra K.C. Epidemiology of renal cell carcinoma World J Oncol 11 2020 79 87 32494314 10.14740/wjon1279 PMC7239575 12 Escudier B. Porta C. Schmidinger M. Renal cell carcinoma: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up Ann Oncol 30 2019 706 720 30788497 10.1093/annonc/mdz056 13 Guo J. Ma J. Sun Y. Chinese guidelines on the management of renal cell carcinoma (2015 edition) Ann Transl Med 3 2015 279 26697439 10.3978/j.issn.2305-5839.2015.11.21 PMC4671863 14 Naito S. Tomita Y. Rha S.Y. Kidney cancer working group report Jpn J Clin Oncol 40 Suppl 1 2010 i51 i56 20870920 10.1093/jjco/hyq127 15 Chinese guidelines for diagnosis and treatment of renal cell carcinoma 2018 (English version) Chin J Cancer Res 31 2019 29 48 30996565 10.21147/j.issn.1000-9604.2019.01.02 PMC6433580 16 Batra U. Parikh P.M. Prabhash K. Oncology Gold Standard™ practical consensus recommendations 2016 for treatment of advanced clear cell renal cell South Asian J Cancer 5 2016 165 167 10.4103/2278-330X.189933 PMC5184749 28032079 17 Singapore Cancer Network (SCAN) Genitourinary Cancer Workgroup Singapore Cancer Network (SCAN) Guidelines for Systemic Therapy of Metastatic Renal Cell Carcinoma (mRCC) Ann Acad Med Singap 44 2015 406 414 26763058 18 Taiwan Urological Association Guidelines In Edition 2020 Available at <http://eschool.tua.org.tw/media/10867> 19 eUpdate – Renal Cell Carcinoma Algorithm. In Edition Available at <https://www.esmo.org/guidelines/genitourinary-cancers/renal-cell-carcinoma/eupdate-renal-cell-carcinoma-algorithm> 20 Powles T. Committee E.G. Recent eUpdate to the ESMO Clinical Practice Guidelines on renal cell carcinoma on cabozantinib and nivolumab for first-line clear cell renal cancer: Renal cell carcinoma: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up Ann Oncol 32 2021 422 423 33271289 10.1016/j.annonc.2020.11.016 21 Dykewicz C.A. Summary of the guidelines for preventing opportunistic infections among hematopoietic stem cell transplant recipients Clin Infect Dis 33 2001 139 144 11418871 10.1086/321805 22 Choueiri T.K. Powles T. Burotto M. Nivolumab plus cabozantinib versus sunitinib for advanced renal-cell carcinoma N Engl J Med 384 2021 829 841 33657295 10.1056/NEJMoa2026982 PMC8436591 23 Motzer R.J. Alekseev B. Rha S.-Y. Lenvatinib plus pembrolizumab or everolimus for advanced renal cell carcinoma N Engl J Med 384 2021 1289 1300 33616314 10.1056/NEJMoa2035716 24 Rini B.I. Plimack E.R. Stus V. Pembrolizumab plus axitinib versus sunitinib for advanced renal-cell carcinoma N Engl J Med 380 2019 1116 1127 30779529 10.1056/NEJMoa1816714 25 Chahoud J. Msaouel P. Campbell M.T. Nivolumab for the treatment of patients with metastatic non-clear cell renal cell carcinoma (nccRCC): A single-institutional experience and literature meta-analysis Oncologist 25 2020 252 258 32162795 10.1634/theoncologist.2019-0372 PMC7066696 26 Choueiri T.K. Heng D.Y.C. Lee J.L. Efficacy of savolitinib vs sunitinib in patients with MET-driven papillary renal cell carcinoma: The SAVOIR phase 3 randomized clinical trial JAMA Oncol 6 2020 1247 1255 32469384 10.1001/jamaoncol.2020.2218 PMC7260692 27 Powles T. Albiges L. Bex A. ESMO Clinical Practice Guideline update on the use of immunotherapy in early stage and advanced renal cell carcinoma Ann Oncol 2021 10.1016/annonc.2021.09.014 34597799 28 Marconi L. Dabestani S. Lam T.B. Systematic review and meta-analysis of diagnostic accuracy of percutaneous renal tumour biopsy Eur Urol 69 2016 660 673 26323946 10.1016/j.eururo.2015.07.072 29 Volpe A. Kachura J.R. Geddie W.R. Techniques, safety and accuracy of sampling of renal tumors by fine needle aspiration and core biopsy J Urol 178 2007 379 386 17561170 10.1016/j.juro.2007.03.131 30 Delahunt B. Cheville J.C. Martignoni G. The International Society of Urological Pathology (ISUP) grading system for renal cell carcinoma and other prognostic parameters Am J Surg Pathol 37 2013 1490 1504 24025520 10.1097/PAS.0b013e318299f0fb 31 Brierley J.G. Wittekind C. IUCN TNM Classification of Malignant Tumours 8th ed. 2016 John Wiley and Sons Inc. New Jersey, USA 32 Dabestani S. Beisland C. Stewart G.D. Long-term outcomes of follow-up for initially localised clear

cell renal cell carcinoma: RECUR database analysis *Eur Urol Focus* 5 2019 857 866 29525381 10.1016/j.euf.2018.02.010 33 Poprach A. Holanek M. Chloupkova R. Cytoreductive nephrectomy and overall survival of patients with metastatic renal cell carcinoma treated with targeted therapy-Data from the National Renis Registry Cancers (Basel) 12 2020 2911 10.3390/cancers12102911 PMC7601448 33050532 34 Umbreit E.C. McIntosh A.G. Suk-Ouichai C. The current role of cytoreductive nephrectomy for metastatic renal cell carcinoma *Indian J Urol* 37 2021 13 19 33850351 10.4103/iju.IJU_293_20 PMC8033221 35 You D. Jeong I.G. Ahn J.H. The value of cytoreductive nephrectomy for metastatic renal cell carcinoma in the era of targeted therapy *J Urol* 185 2011 54 59 21074811 10.1016/j.juro.2010.09.018 36 Esagian S.M. Ziogas I.A. Kosmidis D. Long-term survival outcomes of cytoreductive nephrectomy combined with targeted therapy for metastatic renal cell carcinoma: A systematic review and individual patient data meta-analysis *Cancers (Basel)* 13 2021 695 33572149 10.3390/cancers13040695 PMC7915816 37 Flanigan R.C. Mickisch G. Sylvester R. Cytoreductive nephrectomy in patients with metastatic renal cancer: a combined analysis *J Urol* 171 2004 1071 1076 14767273 10.1097/01.ju.0000110610.61545.ae 38 Bex A. Mulders P. Jewett M. Comparison of immediate vs deferred cytoreductive nephrectomy in patients with synchronous metastatic renal cell carcinoma receiving sunitinib: The SURTIME randomized clinical trial *JAMA Oncol* 5 2019 164 170 30543350 10.1001/jamaoncol.2018.5543 PMC6439568 39 Mejean A. Ravaud A. Thezenas S. Sunitinib alone or after nephrectomy in metastatic renal-cell carcinoma *N Engl J Med* 379 2018 417 427 29860937 10.1056/NEJMoa1803675 40 Altoos B. Amini A. Yacoub M. Local control rates of metastatic renal cell carcinoma (RCC) to thoracic, abdominal and soft tissue lesions using stereotactic body radiotherapy (SBRT) *Radiat Oncol* 10 2015 218 26510665 10.1186/s13014-015-0528-z PMC4625576 41 Lee J. Hodgson D. Chow E. A phase II trial of palliative radiotherapy for metastatic renal cell carcinoma *Cancer* 104 2005 1894 1900 16177996 10.1002/cncr.21410 42 Goyal L.K. Suh J.H. Reddy C.A. The role of whole brain radiotherapy and stereotactic radiosurgery on brain metastases from renal cell carcinoma *Int J Radiat Oncol Biol Phys* 47 2000 1007 1012 10863072 10.1016/s0360-3016(00)00536-8 43 Kim Y.H. Kim J.W. Chung H.-T. Brain metastasis from renal cell carcinoma *Prog Neurol Surg* 25 2012 163 175 22236678 10.1159/000331190 44 Klausner G. Troussier I. Biau J. Stereotactic radiation therapy for renal cell carcinoma brain metastases in the tyrosine kinase inhibitors era: Outcomes of 120 patients *Clin Genitourin Cancer* 17 2019 191 200 30926219 10.1016/j.clgc.2019.02.007 45 Motzer R.J. Escudier B. McDermott D.F. Nivolumab versus everolimus in advanced renal-cell carcinoma *N Engl J Med* 373 2015 1803 1813 26406148 10.1056/NEJMoa1510665 PMC5719487 46 Motzer R.J. Penkov K. Haanen J. Avelumab plus axitinib versus sunitinib for advanced renal-cell carcinoma *N Engl J Med* 380 2019 1103 1115 30779531 10.1056/NEJMoa1816047 PMC6716603 47 Motzer R.J. Rini B.I. McDermott D.F. Nivolumab plus ipilimumab versus sunitinib in first-line treatment for advanced renal cell carcinoma: extended follow-up of efficacy and safety results from a randomised, controlled, phase 3 trial *Lancet Oncol* 20 2019 1370 1385 31427204 10.1016/S1470-2045(19)30413-9 PMC7497870 48 Motzer R.J. Tannir N.M. McDermott D.F. Nivolumab plus ipilimumab versus sunitinib in advanced renal-cell carcinoma *N Engl J Med* 378 2018 1277 1290 29562145 10.1056/NEJMoa1712126 PMC5972549 49 Bruchbacher A. Lemberger U. Hassler M. PD1/PD-L1 therapy in metastatic renal cell carcinoma *Curr Opin Urol* 30 2020 543 551 10.1097/MOU.0000000000000788 32453005 50 Quhal F. Mori K. Bruchbacher A. First-line immunotherapy-based combinations for metastatic renal cell carcinoma: A systematic review and network meta-analysis *Eur Urol Oncol* 4 2021 755 765 33757737 10.1016/j.euo.2021.03.001 51 Harada K. Nozawa M. Uemura M. Treatment patterns and outcomes in patients with unresectable or metastatic renal cell carcinoma in Japan *Int J Urol* 26 2019 202 210 30345560 10.1111/iju.13830 52 Hinata N. Yonese J. Masui S. A multicenter retrospective study of nivolumab monotherapy in previously treated metastatic renal cell carcinoma patients: interim analysis of Japanese real-world data *Int J Clin Oncol* 25 2020 1533 1542 32519026 10.1007/s10147-020-01692-z PMC7392942 53 Sugiyama S. Sato K. Shibasaki Y. Real-world use of temsirolimus in Japanese patients with unresectable or metastatic renal cell carcinoma: recent consideration based on the results of a post-marketing, all-case surveillance study *Jpn J Clin Oncol* 50 2020 940 947 32458996 10.1093/jjco/hyaa062 PMC7401718 54 Tan X. Liu Y. Hou J. Cao G. Targeted therapies for renal cell carcinoma in Chinese patients: focus on everolimus *Onco Targets Ther* 8 2015 313 321 25674006 10.2147/OTT.S64660 PMC4321650 55 Wang Y. Choueiri T.K. Lee J.L. Anti-VEGF therapy in mRCC: differences between Asian and non-Asian patients *Br J Cancer* 110 2014 1433 1437 24548864 10.1038/bjc.2014.28 PMC3960609 56 Numakura K. Horikawa Y.

Kamada S. Efficacy of anti-PD-1 antibody nivolumab in Japanese patients with metastatic renal cell carcinoma: A retrospective multicenter analysis *Mol Clin Oncol* 11 2019 320 324 31341623 10.3892/mco.2019.1887 PMC6636209 57 Powles T. Plimack E.R. Soulieres D. Pembrolizumab plus axitinib versus sunitinib monotherapy as first-line treatment of advanced renal cell carcinoma (KEYNOTE-426): extended follow-up from a randomised, open-label, phase 3 trial *Lancet Oncol* 21 2020 1563 1573 33284113 10.1016/S1470-2045(20)30436-8 58 Motzer R.J. Hutson T.E. Tomczak P. Sunitinib versus interferon alfa in metastatic renal-cell carcinoma *N Engl J Med* 356 2007 115 124 17215529 10.1056/NEJMoa065044 59 Motzer R.J. Hutson T.E. Cella D. Pazopanib versus sunitinib in metastatic renal-cell carcinoma *N Engl J Med* 369 2013 722 731 23964934 10.1056/NEJMoa1303989 60 Motzer R.J. Nosov D. Eisen T. Tivozanib versus sorafenib as initial targeted therapy for patients with metastatic renal cell carcinoma: results from a phase III trial *J Clin Oncol* 31 2013 3791 3799 24019545 10.1200/JCO.2012.47.4940 PMC5569677 61 Choueiri T.K. Hessel C. Halabi S. Cabozantinib versus sunitinib as initial therapy for metastatic renal cell carcinoma of intermediate or poor risk (Alliance A031203 CABOSUN randomised trial): Progression-free survival by independent review and overall survival update *Eur J Cancer* 94 2018 115 125 29550566 10.1016/j.ejca.2018.02.012 PMC6057479 62 Rini B.I. Dorff T.B. Elson P. Active surveillance in metastatic renal-cell carcinoma: a prospective, phase 2 trial *Lancet Oncol* 17 2016 1317 1324 27498080 10.1016/S1470-2045(16)30196-6 PMC9199453 63 Rini B.I. Powles T. Atkins M.B. Atezolizumab plus bevacizumab versus sunitinib in patients with previously untreated metastatic renal cell carcinoma (IMmotion151): a multicentre, open-label, phase 3, randomised controlled trial *Lancet* 393 2019 2404 2415 31079938 10.1016/S0140-6736(19)30723-8 64 Ornstein M.C. Pal S.K. Wood L.S. Individualised axitinib regimen for patients with metastatic renal cell carcinoma after treatment with checkpoint inhibitors: a multicentre, single-arm, phase 2 study *Lancet Oncol* 20 2019 1386 1394 31427205 10.1016/S1470-2045(19)30513-3 65 Powles T. Motzer R.J. Escudier B. Outcomes based on prior therapy in the phase 3 METEOR trial of cabozantinib versus everolimus in advanced renal cell carcinoma *Br J Cancer* 119 2018 663 669 30197417 10.1038/s41416-018-0164-0 PMC6173766 66 Rini B.I. Pal S.K. Escudier B.J. Tivozanib versus sorafenib in patients with advanced renal cell carcinoma (TIVO-3): a phase 3, multicentre, randomised, controlled, open-label study *Lancet Oncol* 21 2020 95 104 31810797 10.1016/S1470-2045(19)30735-1 67 Armstrong A.J. Halabi S. Eisen T. Everolimus versus sunitinib for patients with metastatic non-clear cell renal cell carcinoma (ASPEN): a multicentre, open-label, randomised phase 2 trial *Lancet Oncol* 17 2016 378 388 26794930 10.1016/S1470-2045(15)00515-X PMC6863151 68 Schoffski P. Wozniak A. Escudier B. Crizotinib achieves long-lasting disease control in advanced papillary renal-cell carcinoma type 1 patients with MET mutations or amplification. EORTC 90101 CREATE trial *Eur J Cancer* 87 2017 147 163 29149761 10.1016/j.ejca.2017.10.014 69 Tannir N.M. Jonasch E. Albiges L. Everolimus versus sunitinib prospective evaluation in metastatic non-clear cell renal cell carcinoma (ESPN): A randomized multicenter phase 2 trial *Eur Urol* 69 2016 866 874 26626617 10.1016/j.eururo.2015.10.049 PMC4879109 70 Borchelli D. Barthélémy P. Cabozantinib: a new first-line option for papillary renal cell carcinoma? *Lancet* 397 2021 645 647 33592177 10.1016/S0140-6736(21)00316-0 71 Zoumpourlis P. Genovese G. Tannir N.M. Systemic therapies for the management of non-clear cell renal cell carcinoma: What works, what doesn't, and what the future holds *Clin Genitourin Cancer* 19 2021 103 116 33358151 10.1016/j.clgc.2020.11.005 PMC8169717 72 Pal S.K. Tangen C. Thompson I.M. Jr. A comparison of sunitinib with cabozantinib, crizotinib, and savolitinib for treatment of advanced papillary renal cell carcinoma: a randomised, open-label, phase 2 trial *Lancet* 397 2021 695 703 33592176 10.1016/S0140-6736(21)00152-5 PMC8687736 73 Choueiri T.K. Chin-Heng D.Y. Lee J.-L. SAVOIR: A phase III study of savolitinib versus sunitinib in pts with MET-driven papillary renal cell carcinoma (PRCC) *J Clin Oncol* 38 2020 abstr 5002 74 Albiges L. Tannir N.M. Burotto M. Nivolumab plus ipilimumab versus sunitinib for first-line treatment of advanced renal cell carcinoma: extended 4-year follow-up of the phase III CheckMate 214 trial *ESMO Open* 5 2020 e001079 33246931 10.1136/esmoopen-2020-001079 PMC7703447 75 Tannir N.M. Signoretti S. Choueiri T.K. Efficacy and safety of nivolumab plus ipilimumab versus sunitinib in first-line treatment of patients with advanced sarcomatoid renal cell carcinoma *Clin Cancer Res* 27 2021 78 86 32873572 10.1158/1078-0432.CCR-20-2063 PMC8589223 76 Chen R.C. Choueiri T.K. Feuille M. Quality-adjusted survival with first-line cabozantinib or sunitinib for advanced renal cell carcinoma in the CABOSUN randomized clinical trial (Alliance) *Cancer* 126 2020 5311 5318 33022096

10.1002/cncr.33169 PMC7756547 77 George D.J. Hessel C. Halabi S. Cabozantinib versus sunitinib for untreated patients with advanced renal cell carcinoma of intermediate or poor risk: Subgroup analysis of the Alliance A031203 CABOSUN trial *Oncologist* 24 2019 1497 1501 31399500 10.1634/theoncologist.2019-0316 PMC6853096 78 Choueiri T.K. Motzer R.J. Rini B.I. Updated efficacy results from the JAVELIN Renal 101 trial: first-line avelumab plus axitinib versus sunitinib in patients with advanced renal cell carcinoma *Ann Oncol* 31 2020 1030 1039 32339648 10.1016/j.annonc.2020.04.010 PMC8436592 79 Cella D. Grunwald V. Escudier B. Patient-reported outcomes of patients with advanced renal cell carcinoma treated with nivolumab plus ipilimumab versus sunitinib (CheckMate 214): a randomised, phase 3 trial *Lancet Oncol* 20 2019 297 310 30658932 10.1016/S1470-2045(18)30778-2 PMC6701190 80 Motzer R.J. Escudier B. McDermott D.F. Survival outcomes and independent response assessment with nivolumab plus ipilimumab versus sunitinib in patients with advanced renal cell carcinoma: 42-month follow-up of a randomized phase 3 clinical trial *J Immunother Cancer* 8 2020 e000891 32661118 10.1136/jitc-2020-000891 PMC7359377 81 Cella D. Escudier B. Rini B. Patient-reported outcomes for axitinib vs sorafenib in metastatic renal cell carcinoma: phase III (AXIS) trial *Br J Cancer* 108 2013 1571 1578 23579211 10.1038/bjc.2013.145 PMC3668468 82 Motzer R.J. Escudier B. Tomczak P. Axitinib versus sorafenib as second-line treatment for advanced renal cell carcinoma: overall survival analysis and updated results from a randomised phase 3 trial *Lancet Oncol* 14 2013 552 562 23598172 10.1016/S1470-2045(13)70093-7 83 Cella D. Escudier B. Tannir N.M. Quality of life outcomes for cabozantinib versus everolimus in patients with metastatic renal cell carcinoma: METEOR phase III randomized trial *J Clin Oncol* 36 2018 757 764 29377755 10.1200/JCO.2017.75.2170 PMC6804841 84 Choueiri T.K. Escudier B. Powles T. Cabozantinib versus everolimus in advanced renal-cell carcinoma *N Engl J Med* 373 2015 1814 1823 26406150 10.1056/NEJMoa1510016 PMC5024539 85 Cella D. Grunwald V. Nathan P. Quality of life in patients with advanced renal cell carcinoma given nivolumab versus everolimus in CheckMate 025: a randomised, open-label, phase 3 trial *Lancet Oncol* 17 2016 994 1003 27283863 10.1016/S1470-2045(16)30125-5 PMC5521044 86 Motzer R.J. Hutson T.E. Glen H. Lenvatinib, everolimus, and the combination in patients with metastatic renal cell carcinoma: a randomised, phase 2, open-label, multicentre trial *Lancet Oncol* 16 2015 1473 1482 26482279 10.1016/S1470-2045(15)00290-9 87 Cherny N.I. Dafni U. Bogaerts J. ESMO-magnitude of clinical benefit scale version 1.1 *Ann Oncol* 28 2017 2340 2366 28945867 10.1093/annonc/mdx310 88 Gyawali B. de Vries E.G.E. Dafni U. Biases in study design, implementation, and data analysis that distort the appraisal of clinical benefit and ESMO-Magnitude of Clinical Benefit Scale (ESMO-MCBS) scoring *ESMO Open* 6 2021 100117 33887690 10.1016/j.esmoop.2021.100117 PMC8086024 Supplementary data Supplementary Material Supplementary Tables

The authors thank Ms K. Marinoni and Ms D. Young from the Scientific and Medical Division of ESMO, Ms Z. Othman from the ESMO Singapore Office, Dr A. Tan from the LPG Asia Alumni, and Ms H. W. Goh and colleagues of the IT vendor Globewerks for their assistance in the execution of the 'face-to-face' virtual meeting of experts. Dr A. Kinsella of Cancer Communications and Consultancy Ltd, Knutsford, Cheshire, UK is acknowledged for her contribution to the preparation of the manuscript. Mrs N. Latino, ESMO Head of Scientific Affairs, is acknowledged for her contribution in the completion of the ESMO-MCBS table.

No external funding has been received for the preparation of these guidelines. Production costs have been covered by 10.13039/501100007075 ESMO, Switzerland from central funds.

RK declares institutional payments from Pfizer, Merck Sharp & Dohme (MSD), Bristol Myers Squibb (BMS), Eisai, Amgen, Astellas, Johnson & Johnson (J&J), Novartis and Merck, support for meeting attendance or travel from Pfizer, MSD, BMS, Eisai, Amgen, Astellas, J&J, Novartis and Merck. CP declares consulting fees from AstraZeneca, BMS, Eisai, EUSA Pharma, Ipsen, Merck, MSD, Novartis and Pfizer, payment or honoraria from Angelini Pharma, AstraZeneca, BMS, Eisai, EUSA Pharma, General Electric, Ipsen, Janssen, Merck, MSD, Novartis and Pfizer, support for attending meetings and/or travel from Roche. AW declares personal fees from MS, MSD, Pfizer, EISAI and IPSEN, participation on a data safety monitoring or advisory board for BMS, MSD, Pfizer, EISAI, IPSEN. TP declares research funding from Merck Serono, MSD, Roche, BMS, AstraZeneca,

Astellas, Novartis, J&J, Seattle Genetics, Pfizer, Exelixis and Eisai, honoraria from Merck Serono, MSD, Roche, BMS, AstraZeneca, Astellas, Novartis, J&J, Seattle Genetics, Pfizer, Exelixis and Eisai. QSN declares support for attending meetings and/or travel from BMS, Boehringer Ingelheim, MSD and Astellas, participation on a data safety monitoring or advisory board for MSD and Boehringer Ingelheim. MSc declares honoraria from BMS, MSD, Merck, Roche, Pfizer, EUSA, EISAI, EXELIXIS and Ipsen, consulting fees from BMS, MSD, Merck, Roche, Pfizer, EUSA, EISAI, EXELIXIS and Ipsen, support for attending meetings and/or travel from BMS, Roche, Pfizer and Ipsen, participation on a data or safety monitoring board for BMS, MSD, Merck, Roche, Pfizer, EUSA, EISAI, EXELIXIS and Ipsen. YM declares payments or honoraria from BMS, MSD and Takeda, participation on an advisory board for Chugai Pharmaceutical and Takeda, local PI, institutional, financial interest from MSD. JL declares grants or contracts from Pfizer, Ipsen, BMS, MSD, Merck, Roche, AstraZeneca, Seattle Genetics, participation on a data safety monitoring or advisory board from Pfizer Korea, Astella Korea, BMS, Merck, MSD, AstraZeneca, stocks or stock options from Myovant Sciences, Amgen, J&J and Merck. FC declares payment for educational events from Eisai and Pfizer, receipt of equipment for a patient sampling programme from Pfizer. Y-SP declares honoraria and consulting fees from MSD, Roche, Merck, Ipsen, BMS/ONO, Novartis, Pfizer, Astellas, Janssen and GlaxoSmithKline (GSK), support for attending meetings and/or travel from Ipsen, BMS/ONO, Novartis, Pfizer, Astellas and Janssen. MSa declares research grants from Roche and MSD, payments or honoraria from MSD, Novartis, Roche, Pfizer, Eisai, Novartis, AstraZeneca, Amgen and Ipsen, receipt of equipment/materials for a compassionate programme for drugs/drug samples from Pfizer, AstraZeneca, Novartis, Ipsen, Eisai and MSD. HL declares payment or honoraria from MSD, Amgen, Astellas and IPSEN, participation on a data safety monitoring or advisory board for MSD and Astellas. HK declares payment or honoraria from BMS, MSD, Merck Biopharma, Takeda and Pfizer. GSB (deceased). GC declares institutional grants from Merck, consulting fees from BMS, Pfizer, MSD, AstraZeneca, Daiichi Sankyo, Lilly, Novartis and Seattle Genetics, payment or honoraria from AstraZeneca, Roche and Daiichi Sankyo. SC declares consulting fees from BMS, AstraZeneca, MSD, Roche and Servier, payment or honoraria from BMS, AstraZeneca, Roche, Ipsen, MSD Eisai and Bayer, consulting fees from BMS, AstraZeneca, MSD, Roche and Servier and stock or stock options in BMS and Agenus Oncology. SP declares fees for consultancy/advisory roles from AbbVie, Amgen, AstraZeneca, Bayer, Beigene, Biocartis, Boehringer Ingelheim, BMS, Clovis, Daiichi Sankyo, Debiopharm, ecancer, Eli Lilly, Elsevier, Foundation Medicine, Illumina, Imedex, Incyte, Janssen, Medscape, MSD, Merck Serono, Merrimack, Novartis, Pharma Mar, Phosphatidylcholine Therapeutics, PER, Pfizer, PRIME, Regeneron, Roche/Genentech, RTP, Sanofi, Seattle Genetics, Takeda, speaker roles for AstraZeneca, Boehringer Ingelheim, BMS, ecancer, Eli Lilly, Illumina, Imedex, Medscape, MSD, Novartis, PER, Pfizer, Prime, Roche/Genentech, RTP, Sanofi, Takeda and the receipt of grants/research support: (Sub) investigator in trials (institutional financial support for trials) sponsored by Amgen, AstraZeneca, Biodesix, Boehringer Ingelheim, BMS, Clovis, GSK, Illumina, Lilly, MSD, Merck Serono, Mirati, Novartis, and Pfizer, Phosphatidylcholine Therapeutics, Roche/Genentech. TY declares institutional grants or contracts from Taiho Pharmaceuticals, Sumitomo Dainippon, Ono Pharmaceuticals, Chugai Pharmaceuticals, Amgen, Parexel International, MSD, Daiichi Sankyo, and Sanofi. All other authors have declared no conflicts of interest. See also ICMJE forms.