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SPECIAL ARTICLE

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

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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.

Key words: ESMO, guidelines, kidney cancer, Pan-Asian, renal cell carcinoma treatment

INTRODUCTION

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.[7-9] A study of the incidence and mortality rates for kidney cancer in Asia

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†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.

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,[13-18] 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.

METHODOLOGY

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.

RESULTS

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,[22-26] 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.

1. Diagnosis and pathology/molecular biology—Recommendations 1a–d

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%].**

1b. For accurate staging, US and contrast-enhanced chest, abdominal and pelvic CT scans are recommended [III, A].

1c. 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].

1d. Pathology should be assessed using the 2016 World Health Organization histological classification of renal tumours and ISUP grading.[30]

2. Staging and risk assessment—Recommendation 2

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]

3. Management of local/locoregional disease—Recommendations 3a–g

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].

3b. In patients with compromised renal function, solitary or bilateral tumours, PN is also recommended with no tumour size limitation.

3c. 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

Table 1. Summary of Asian recommendations

Recommendations	Acceptability consensus (%)
Recommendation 1: diagnosis and pathology/molecular biology	
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) [V, B]**.	100
1b. For accurate staging, US and contrast-enhanced chest, abdominal and pelvic CT scans are recommended [III, A].	100
1c. A renal tumour core biopsy is recommended before treatment with ablative therapies and in patients with metastatic disease before starting systemic treatment [III, B].	100
1d. Pathology should be assessed using the 2016 WHO histological classification of renal tumours and International Society of Urological Pathology grading.	100
Recommendation 2: staging and risk assessment	
2. The UICC TNM 8 staging system should be used.	100
Recommendation 3: management of local/locoregional disease	
3a. For organ confined T1 tumours $<$7 cm, partial nephrectomy is recommended [I, A]. Laparoscopic radical nephrectomy is recommended if partial nephrectomy is not feasible [I, A].	100
3b. In patients with compromised renal function, solitary or bilateral tumours, partial nephrectomy is also recommended with no tumour size limitation.	100
3c. Radiofrequency ablation, microwave ablation or cryoablation are options in patients with small cortical tumours ($\leq$3 cm), frail patients, high surgical risk, solitary kidney, compromised renal function and hereditary RCC or bilateral tumours [III, B].	100
3d. **When nephrectomy is not contemplated or possible,** a renal biopsy is recommended to confirm malignancy and histopathological subtype **[V, C].**	100
3e. Active surveillance **may be selected** for elderly patients with significant comorbidities or those with a short life expectancy and solid renal tumours $<$40 mm [II, B]; renal biopsy is recommended to select these patients.	100
3f. For T2 tumours $>$7 cm, laparoscopic radical nephrectomy is the preferred option.	100
3g. For T3 and T4 tumours (locally advanced), open radical nephrectomy is the standard of care, although a laparoscopic approach can be considered.	100
Recommendation 4: management of advanced/metastatic disease	
Ablative therapy	
4a. Cytoreductive nephrectomy is recommended in patients with good PS, **low metastatic burden and/or symptomatic primary tumours either as up-front surgery or delayed nephrectomy [III, B].**	100
4b. Image-guided RT techniques such as volumetric-modulated arc therapy or stereotactic body radiotherapy are needed to enable the delivery of a high dose [IV, B].	100
4c. Radiotherapy 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 bones or brain [III, A].	100
4d. For mRCC patients with brain metastases, the use of corticosteroids can provide temporary relief of cerebral symptoms. Whole-brain radiotherapy between 20 and 30 Gy in 4-10 fractions is recommended for effective symptom control [II, B].	100
4e. For mRCC patients with a **limited number of** brain metastases, **surgery and/or** stereotactic radiosurgery with or without whole-brain radiotherapy should be considered [II, A].	100
Systemic therapy	
First-line systemic treatment	
4f. The combination of axitinib and pembrolizumab **is recommended** as a first-line therapeutic option for patients with advanced disease, irrespective of IMDC prognostic subgroups and PD-L1 biomarker status [I, A; ESMO-MCBS v1.1 score: 4].	100
4g. The combination of cabozantinib and nivolumab is recommended as a first-line therapeutic option for advanced disease **irrespective o**f IMDC **prognostic subgroup and PD-L1 biomarker status** [I, A; ESMO-MCBS v1.1 score: 4].	100
4h. Lenvatinib and pembrolizumab join the other VEGFR/PD-1-targeting combinations (axitinib and pembrolizumab or nivolumab and cabozantinib) to be recommended as a first-line treatment option for patients with advanced ccRCC, **irrespective of** the IMDC **subgroup and PD-L1 biomarker status** [I, A; ESMO-MCBS v1.1 score: 4]. The combination of ipilimumab and nivolumab 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].	100
4i. Sunitinib [I, A], pazopanib [I, A], and tivozanib [II, B] 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-risk [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].].	100
4j. 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 RCTs. Pazopanib was found to be non-inferior to sunitinib in the COMPARZ study [III, C; ESMO-MCBS v1.1 score: 4].	100
4k. Active surveillance is an alternative approach in a small subset of patients. This requires careful consideration in patients with good prognostic features [III, B].	100
4l. Axitinib and avelumab, and bevacizumab and atezolizumab, are not yet associated with an overall survival advantage and are therefore not recommended [I, C].	100
4m. Cessation of immune checkpoint inhibitors can be considered after 2 years of therapy in selected patients with good disease control [IV, B].	100
Second-line systemic treatment	
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].	100
4o. 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].	100
4p. 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**.	100

Continued

Table 1. Continued

Recommendations	Acceptability consensus (%)
4q. Sequencing VEGFR TKI therapy after PD-1-based first-line therapy is associated with modest response rates. Thus, patients should receive a VEGFR-targeted agent that they have not received previously [III, A]	100
4r. RCT data to support continued immune checkpoint inhibition after established progression is lacking and hence it is not recommended.	100
Non-ccRCC	100
4s. Cabozantinib is the preferred first-line agent in patients with advanced papillary RCC who have not undergone additional molecular testing [II, B].	100
4t. Alternative options include sunitinib [II, B] and pembrolizumab [III, B], while in MET-driven tumours, savolitinib can be considered (where available) [III, C].	100
4u. 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].	100
4v. Second-line therapy should focus on those first-line agents that have not been used previously [IV, C].	100
Recommendation 5: follow-up, long-term implications and survivorship	
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	100
5b. For mRCC patients receiving systemic therapy, 2- to 4-month follow-up with a CT scan is advised	100
5c. RECIST is the most frequently used method to assess drug efficacy	100

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.

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.

4. Management of advanced/metastatic disease—Recommendations 4a–v

Ablative therapy. 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.[33-35] 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].

4c. 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].

4d. 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].

4e. 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%].**

First-line systemic treatment. 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 anti-tumour immune response.[45-50] The applicability of these agents to the treatment of Asian patients with mRCC has also been investigated and confirmed.[9,51-56] 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.

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].

4g. 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]

4h. 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]

4i. 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]

4j. 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].

4k. 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]

4l. Axitinib and avelumab,[46] and bevacizumab and atezolizumab,[63] are not yet associated with an OS advantage and are therefore not recommended [I, C].

4m. Cessation of immune checkpoint inhibitors can be considered after 2 years of therapy in selected patients with good disease control. [IV, B].

Second-line systemic treatment. 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].

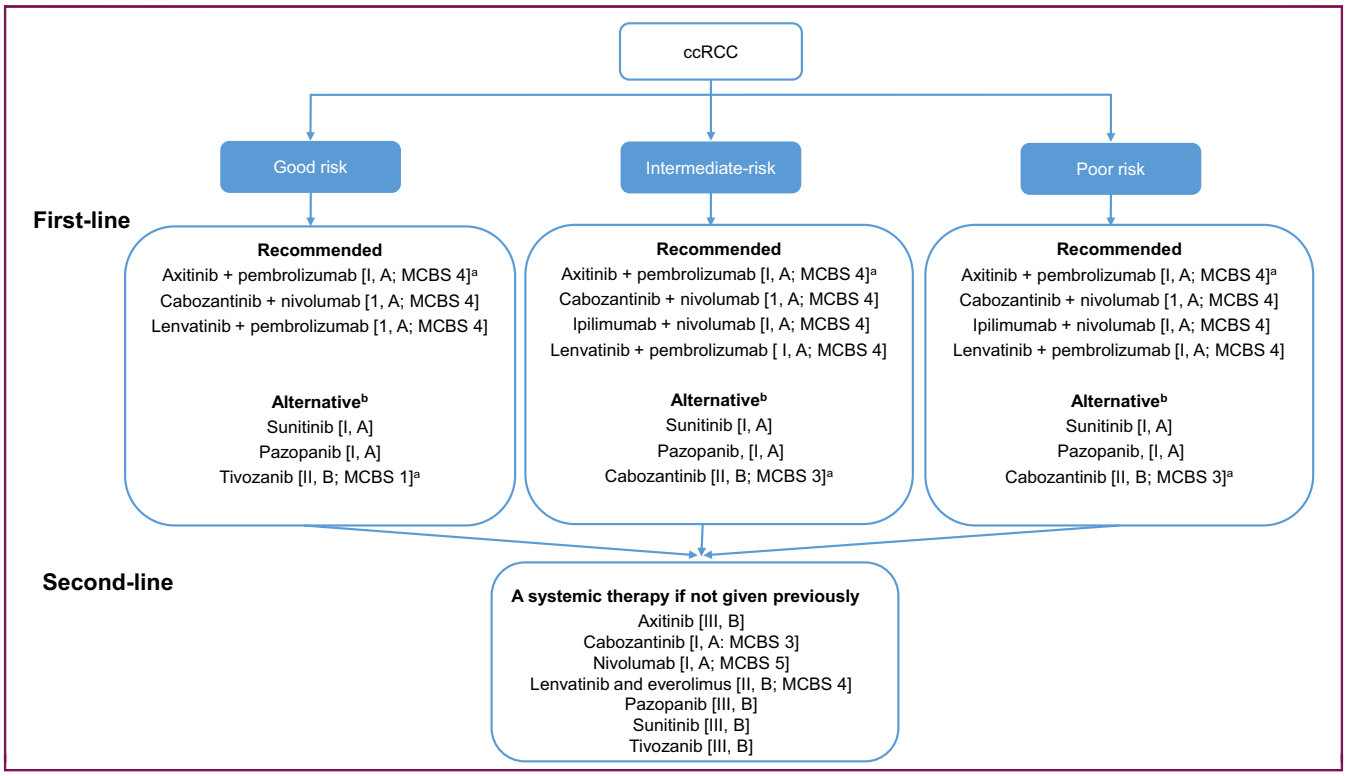

Figure 1. Systemic first-line and subsequent line treatment of ccRCC.
ccRCC, clear cell renal cell carcinoma; EMA, European Medicines Agency; ESMO-MCBS, European Society for Medical Oncology-Magnitude of Clinical Benefit Scale.
[a] ESMO-MCBS scores for new therapies/indications approved by the EMA since 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 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].

4o. 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].

4p. 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.**

4q. Sequencing VEGFR TKI therapy after PD-1-based first-line therapy is associated with modest response rates.[64-66] Thus, patients should receive a VEGFR-targeted agent that they have not received previously [III, A].

4r. RCT data to support continued immune checkpoint inhibition after established progression is lacking, and hence it is not recommended.

Non-ccRCC. Clinical data for the medical treatment of the rarer non-clear cell subtypes of RCC are relatively limited[67-69] 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).

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

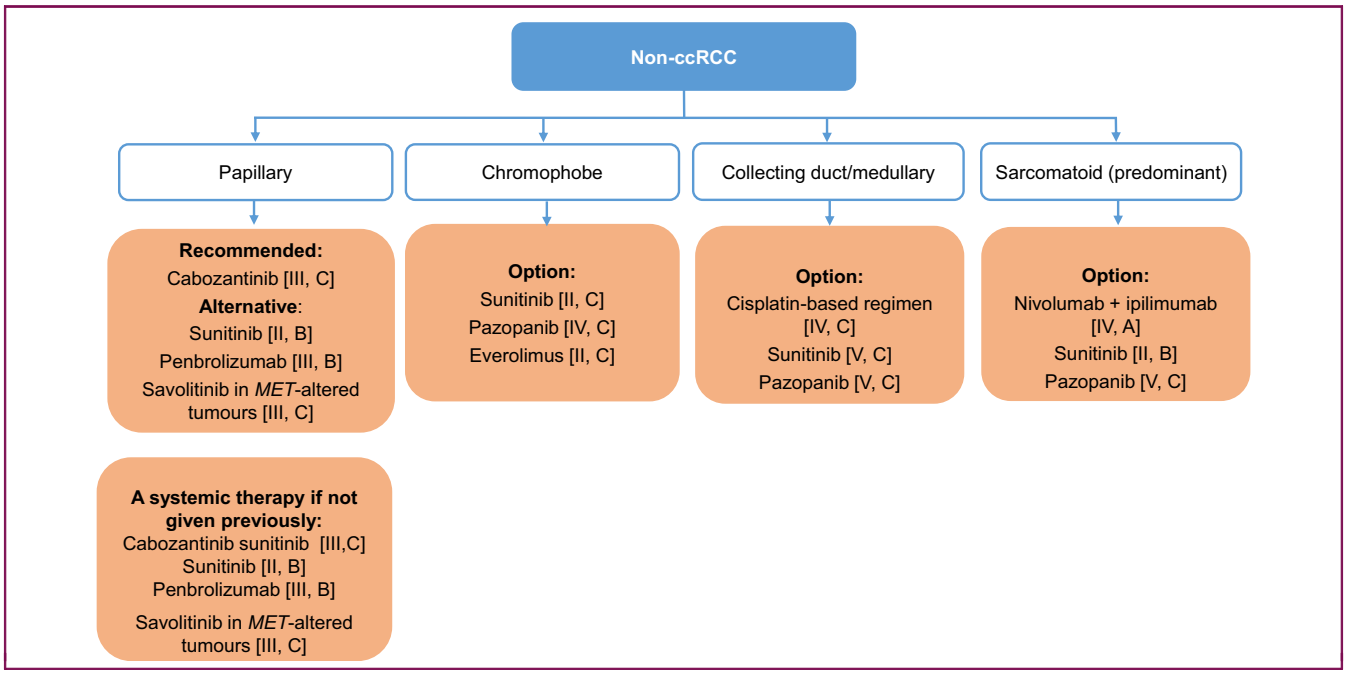

Figure 2. Systemic first-line treatment of non-ccRCC.
MET, mesenchymal-epithelial transition gene; non-ccRCC, non-clear cell renal cell carcinoma.

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].

4t. 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].

4u. Immune checkpoint inhibitor-based therapy is particularly active in sarcomatoid renal tumours and should

Table 2. Summary of applicability (availability) of drugs, equipment and testing according to Asian country

Drugs/equipment	CSCO	ISMPO	JSMO	KSMO	MOS	SSO	TOS
	Available Y/N	Available Y/N	Available Y/N	Available Y/N	Available Y/N	Available Y/N	Available Y/N
Laparoscopic RN	Y	Y	Y	Y	Y	Y	Y
RFA, MWA or CA	Y	Y	N	Y	Y	Y	Y
VMAT or SBRT	Y	Y	Y	Y	Y	Y	Y
SRS	Y	Y	Y	Y	Y	Y	Y
Tivozanib	N	N	N	N	N	N	N
Axitinib and pembrolizumab	Y	Y	Y	Y	Y	Y	Y
Ipilimumab and nivolumab	Y	Y	Y	Y	N	Y	Y
Cabozantinib	Y	N	Y	Y	N	Y	Y
Cabozantinib and nivolumab	Y	Y	N	N	N	Y	Y
Lenvatinib and everolimus	Y	Y	N	Y	Y	Y	Y
Lenvatinib and pembrolizumab	N	Y	N	Y	Y	Y	Y

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.

Table 3. ESMO-MCBS table for new therapies/indications in renal cell carcinoma[a]

Therapy	Disease setting	Trial	Control	Absolute survival gain	HR (95% CI)	QoL/toxicity	ESMO-MCBS score[b]
Cabozantinib	First-line in advanced RCC treatment-naive adults with intermediate or poor risk	Study comparing cabozantinib with commercially supplied sunitinib in patients with previously untreated locally advanced or metastatic RCC (CABOSUN)[61,76,77] Phase II NCT01835158	Sunitinib Median PFS: 5.6 months Median OS: 21.2 months	PFS gain: 2.6 months OS gain: 5.4 months	PFS HR: 0.66 (0.46-0.95) OS HR: 0.80 (0.50-1.26) NS	*Post hoc* Q-TWIST analysis not scorable	3 (Form 2b)
Pazopanib	First-line in metastatic RCC with clear cell component	A study of pazopanib versus sunitinib in the treatment of subjects with locally advanced and/or metastatic RCC (COMPARZ)[59] Phase III NCT00720941	Sunitinib PFS non-inferiority: 9.5 months Median OS: 29.3 months	PFS gain: −1.1 months OS gain: −0.9 months	PFS HR: 1.05 (0.90-1.22) <1.25 non- inferiority threshold for UL 95% CI OS HR: 0.91 (0.76-1.08)	Reduced toxicity	4 (Form 2c)
Tivozanib	First-line treatment of adult patients who are VEGFR and mTOR pathway inhibitor-naive following disease progression after one prior treatment with cytokine therapy.	Tivozanib versus sorafenib in patients with advanced RCC (TIVO-1)[60] Phase III NCT01030783	Sorafenib Median PFS: 9.1 months	PFS gain: 2.8 months	PFS HR: 0.80 (0.64-0.99)	No QoL benefit	1 (Form 2b)
Axitinib in combination with avelumab	First-line treatment of advanced RCC	Study of axitinib in combination with avelumab versus sunitinib monotherapy in the first-line treatment of patients with advanced RCC (JAVELIN Renal 101)[46,78] Phase III NCT02684006	Sunitinib Median PFS ITT: 8.0 months	PFS gain: 5.3 months	PFS HR: 0.69 (0.57-0.83) OS immature		3 (Form 2b)
Axitinib in combination with pembrolizumab	First-line treatment of advanced RCC	Study to evaluate efficacy and safety of axitinib in combination with pembrolizumab versus sunitinib monotherapy as a first-line treatment of locally advanced or metastatic renal cell carcinoma (KEYNOTE-426)[24,57] Phase III NCT02853331	Sunitinib Median PFS: 11.1 months Median OS: 35.7 months	PFS gain: 4.3 months Estimated OS gain: 16.8[d] months	PFS HR: 0.71 (0.60-0.84) OS HR: 0.68 (0.55-0.85)		4[c] (Form 2b)

Continued

https://doi.org/10.1016/j.esmoop.2021.100304

Table 3. Continued

Therapy	Disease setting	Trial	Control	Absolute survival gain	HR (95% CI)	QoL/toxicity	ESMO-MCBS score[b]
Cabozantinib in combination with nivolumab	First-line treatment of advanced RCC	Cabozantinib combined with nivolumab versus sunitinib in participants with previously untreated advanced or metastatic RCC (CheckMate 9ER)[22] Phase III NCT03141177	Sunitinib Median PFS: 8.3 months Median OS: 1 year 75.6%	PFS gain: 8.3 months OS gain: 1 year 10.1% (only 3% still at risk)	PFS HR: 0.51 (0.41-0.64) OS HR: 0.60 (98.89% CI 0.40-0.89) $P = 0.001$ <0.011 threshold for early stopping	QoL benefit reported in exploratory evaluation[e]	4[c,f] (Form 2b)
Lenvatinib in combination with pembrolizumab	First-line treatment of advanced clear cell, RCC	Trial to compare the efficacy and safety of lenvatinib plus pembrolizumab versus lenvatinib plus everolimus versus sunitinib in advanced RCC (CLEAR)[23] Phase III NCT02811861	Sunitinib Median PFS: 9.2 months Median OS: 2 years 70.4%	PFS gain: 14.7 months OS gain: 2 years 8.8%	PFS HR: 0.39 (0.32-0.49) OS HR: 0.66 (0.49-0.88; $P = 0.005$ <0.016 for early stopping		4[f,g] (Form 2b)
Nivolumab in combination with ipilimumab	First-line treatment of intermediate- and poor-risk advanced RCC	Nivolumab combined with ipilimumab versus sunitinib monotherapy in subjects with previously untreated, advanced or metastatic RCC (CheckMate 214)[47,48,74,79,80] Phase III NCT02231749	Sunitinib Median OS: 26.6 months	OS gain: 21.5 months	OS HR: 0.65 (0.54-0.78)	QoL benefit reported in exploratory evaluation[e]	4[c] (Form 2a)
Axitinib	Advanced renal cell carcinoma after failure of prior treatment with sunitinib or a cytokine	Axitinib as second-line therapy for metastatic RCC (AXIS)[66,81,82] Phase III NCT00678392	Sorafenib Median PFS: 4.7 months Median OS: 19.2 months	PFS gain: 2.0 months OS gain: 0.9 month	PFS HR: 0.67 (0.54-0.81) OS HR: 0.97 (0.80-1.17) NS	No QoL benefit Reduced toxicity	4 (Form 2b)
Cabozantinib	Advanced RCC after prior VEGF-targeted therapy	Cabozantinib versus everolimus in subjects with metastatic RCC that has progressed after prior VEGFR TKI therapy (METEOR)[65,83,84] Phase III NCT01865747	Everolimus Median OS: 17.1 months	OS gain: 4.3 months	OS HR: 0.70 (0.58-0.85)	QoL benefit reported in laboratory evaluation[e]	3 (Form 2a)
Nivolumab	Advanced RCC after prior therapy	Nivolumab versus everolimus in subjects with advanced or metastatic clear cell RCC who have received prior antiangiogenic therapy (CheckMate 025)[45,85] Phase III NCT01668784	Everolimus Median OS: 19.6 months	OS gain: 5.4 months	OS HR: 0.73 (0.57-0.93)	Reduced grade 3/4 adverse events QoL benefit reported in laboratory evaluation[e]	5 (Form 2a)

Continued

Table 3. Continued

Therapy	Disease setting	Trial	Control	Absolute survival gain	HR (95% CI)	QoL/toxicity	ESMO-MCBS score[b]
Lenvatinib in combination with everolimus	Unresectable advanced or metastatic RCC previously treated with a VEGF inhibitor	Study of lenvatinib alone, and in combination with everolimus in subjects with unresectable advanced or metastatic RCC following one prior VEGF-targeted treatment[86] Phase II NCT01136733	Everolimus Median OS: 15.4 months	OS gain: 10.1 months	OS HR: 0.51 (0.30-0.88)		4 (Form 2a)

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.

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

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

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

[d] Calculated estimate of gain based on point estimate HR 0.68.

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

[f] 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.

[g] FDA approval March 2021.

be recommended ahead of single-agent VEGFR-targeted therapy [II, A].[22,23,57,74,75]

4v. Second-line therapy should focus on those first-line agents that have not been used previously [IV, C].

5. Follow-up, long-term implications and survivorship—Recommendations 5a–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.

5b. For mRCC patients receiving systemic therapy, 2- to 4-month follow-up with a CT scan is advised.

5c. RECIST is the most frequently used method to assess drug efficacy.

Drug and treatment availability. 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.

CONCLUSIONS

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.

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