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SPECIAL ARTICLE

Pan-Asian adapted ESMO Clinical Practice Guidelines for the diagnosis, treatment and follow-up of patients with metastatic colorectal cancer

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The European Society for Medical Oncology (ESMO) Clinical Practice Guidelines for the diagnosis, treatment and follow-up of patients with metastatic colorectal cancer (mCRC), published in late 2022, were adapted in December 2022, according to previously established standard methodology, to produce the Pan-Asian adapted (PAGA) ESMO consensus guidelines for the management of Asian patients with mCRC. The adapted guidelines presented in this manuscript represent the consensus opinions reached by a panel of Asian experts in the treatment of patients with mCRC representing the oncological societies of China (CSCO), Indonesia (ISHMO), India (ISMPO), Japan (JSMO), Korea (KSMO), Malaysia (MOS), the Philippines (PSMO), Singapore (SSO), Taiwan (TOS) and Thailand (TSCO), co-ordinated by ESMO and the Japanese Society of Medical Oncology (JSMO). The voting was based on scientific evidence and was independent of the current treatment practices, drug access restrictions and reimbursement decisions in the different Asian countries. The latter are discussed separately in the manuscript. The aim is to provide guidance for the optimisation and harmonisation of the management of patients with mCRC across the different countries of Asia, drawing on the evidence provided by both Western and Asian trials, whilst respecting the differences in screening practices, molecular profiling and age and stage at presentation, coupled with a disparity in the drug approvals and reimbursement strategies, between the different countries.

Key words: ESMO, guidelines, Pan-Asian, metastatic colorectal cancer, treatment

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INTRODUCTION

There were an estimated 19.3 million new cases and 10 million cancer deaths worldwide in 2020.[1] Overall, for both sexes combined, colorectal cancer (CRC) globally ranks third as the most commonly diagnosed cancer (10.0% of new cases) and second as a leading cause of cancer death (9.4% of global cancer deaths).[1] For both sexes combined the highest incidence of CRC cases (51.8%) and of CRC deaths (52.4%) are estimated to occur in Asia.[1]

The estimated epidemiology for CRC in Asia for 2018 showed China to have the highest 5-year prevalence, number of new cases and deaths from CRC, followed by, in terms of new cases, Japan, India, Korea, Indonesia, Thailand and the Philippines.[2] The increase in the crude incidence of CRC across Asia can be attributed in large part to an increasingly westernised dietary lifestyle, smoking, high alcohol consumption, physical inactivity, obesity and diabetes and also to increasingly aged populations.[3] On an individual level, China showed an increasing incidence and mortality, Singapore a rising incidence but reduced mortality and Japan a decreasing incidence and mortality.[4] Japan, South Korea, Singapore, Taiwan and certain provinces in China[5-9] have population-based screening programmes which together with the Asia-Pacific consensus recommendations for CRC screening, which involved 13 countries in the Asia-Pacific region,[10] should facilitate an improvement in early tumour detection. Also, recently a Chinese study reported a higher incidence of adenomas in the right- versus left-sided colon (44% versus 39%).[11] Whilst, a Korean study reported a higher proportion of right-sided adenomas in older subjects when compared with younger subjects.[12] Significantly, a multinational study involving Hong Kong, Taiwan, Korea and Japan[13] identified an increasing trend in early-onset (<50 years of age) colon and rectal cancers.

The most recent European Society for Medical Oncology (ESMO) guidelines for the diagnosis treatment and follow up of patients with mCRC were published in 2022,[14] and a decision was taken by ESMO and the Japanese Society of Medical Oncology (JSMO) that these latest ESMO guidelines should be adapted for the management and treatment of patients of Asian ethnicity. This manuscript summarises the Pan-Asian adapted guidelines developed and agreed at a hybrid virtual/face-to-face working meeting that took place in Singapore on 01 December 2022, hosted by JSMO. Each recommendation is accompanied by the level of evidence (LoE), grade of recommendation (GoR) (Supplementary Table S1, available at https://doi.org/10.1016/j.esmoop.2023.101558) and the percentage consensus reached.

METHODOLOGY

This Pan-Asian adaptation of the current ESMO Clinical Practice Guidelines,[14] and associated updates, was prepared in accordance with the principles of ESMO standard operating procedures (https://www.esmo.org/Guidelines/ESMO-Guidelines-Methodology) and was a JSMO-ESMO initiative endorsed by the Chinese Society of Clinical Oncology (CSCO), the Indonesian Society of Hematology and Medical Oncology (ISHMO), the Indian Society of Medical and Paediatric Oncology (ISMPO), the Korean Society of Medical Oncology (KSMO), the Malaysian Oncological Society (MOS), the Philippine Society of Medical Oncology (PSMO), the Singapore Society of Oncology (SSO), the Taiwan Oncology Society (TOS) and the Thailand Society of Clinical Oncology (TSCO). An international panel of experts was selected from the JSMO ($n = 10$), the ESMO ($n = 5$), and two experts from each of the nine other oncological societies. Only two of the six expert members from the JSMO (HB and EO) were allowed to vote on the recommendations together with the experts from each of the nine other Asian oncology societies ($n = 20$). None of the additional JSMO members present and none of the ESMO experts were allowed to vote and were present in an advisory role only (see Supplementary material: Methodology, available at https://doi.org/10.1016/j.esmoop.2023.101558).

RESULTS

A. Scientific adaptations of the ESMO recommendations

In the initial pre-meeting survey, the 20 voting Asian experts reported on the 'acceptability' of the 68 recommendations for the diagnosis, treatment and follow-up of patients with mCRC from the most recent ESMO Clinical Practice Guidelines[14] (Supplementary Table S2, available at https://doi.org/10.1016/j.esmoop.2023.101558), in the five categories outlined in the text below and in Table 1. A lack of agreement in the pre-meeting survey was established for 25 recommendations, 21 of which were discussed at the hybrid virtual/face-to-face face working meeting in Singapore to adapt the recently published ESMO Clinical Practice Guidelines and four after the meeting. Two new recommendations were also added (see Supplementary Material: Results, available at https://doi.org/10.1016/j.esmoop.2023.101558)

1. Diagnosis, pathology and molecular biology—recommendations 1a-k. The Pan-Asian panel of experts agreed with and accepted completely (**100% consensus**) the original ESMO recommendations, 'recommendations 1a-g and 1i, and 1j' (Table 1), without change.

In relation to 'recommendation 1h', however, concern was raised over restricting the recommendation to patients with *RAS* wild-type (wt) disease. Although the trials have mainly been conducted in patients with *RAS* wt disease, the MyPathway study[80] reported a *HER2* amplification in 23% of patients with *RAS*-mutant disease and an overall response rate for these patients of 8% compared with 40% for those with *HER2*-amplified, *RAS* wt disease. Thus, although it was accepted that 'recommendation 1h' should remain unchanged (**100% consensus**) (Table 1), it was agreed that testing for *HER2* amplification should not be excluded for patients with *RAS*-mutant disease but should be conducted subject to resource availability and the reimbursement and diagnostic testing policies of the individual Asian countries.

Table 1. Summary of Asian consensus recommendations for the treatment of patients with mCRC

Recommendations	Acceptability consensus
1: Diagnosis, pathology and molecular biology	
1a. For biomarker testing, fixation with 10% neutral buffered formalin (4% formaldehyde) for no less than 6 h and no more than 48 h is recommended [V, A].	100%
1b. The primary pathologist should review all available tumour specimens and enrich samples by macrodissection to maximise tumour cell content (>20%) before DNA extraction [IV, A].	100%
1c. Testing for MMR status and *KRAS*, *NRAS* exon 2, 3 and 4 and *BRAF* mutations is recommended in all patients at the time of mCRC diagnosis [I, A].	100%
1d. *RAS* testing is mandatory before treatment with anti-EGFR mAbs and can be carried out on either the primary tumour or other metastatic sites[15-17] [III, A].	100%
1e. *BRAF* mutation status should be assessed simultaneously with the evaluation of *RAS*, for prognostic assessment[18] [I, B] and for the option of treatment with cetuximab–encorafenib[19] [I, A].	100%
1f. dMMR/MSI testing in mCRC can assist in genetic counselling for Lynch syndrome [II, B].	100%
1g. dMMR/MSI status is also recommended in the initial molecular workup in metastatic disease for its predictive value for the use of ICIs[20,21] [I, A].	100%
1h. Identification of *HER2* amplification by IHC or FISH is recommended in *RAS* wt patients to detect those who may benefit from HER2 blockade[22] [III, B].	100%
1i. Testing of other biomarkers including *ALK* and *ROS1* gene fusions, mutations of *PIK3CA* and *HER2* activating mutations are not recommended outside clinical trials[23] [IV, D].	100%
1j. In the rare event that an *NTRK* fusion is detected by IHC and/or comprehensive genomic analysis, treatment with larotrectinib or entrectinib is recommended[23-26] [III, A].	100%
1k. **Depending on the anticipated genetic profile of a specific Asian patient population**, DPD genotyping or phenotyping **may be considered** before initiating fluoropyrimidine-based therapy [III, **C**]. **DPD genotyping or phenotyping should be implemented in patients who experience severe fluoropyrimidine toxicity[27] [V]**.	100%
1l. ***UGT1A1* genotyping remains an option and it is recommended that it is carried out in patients with a suspicion of UGT1A1 deficiency as reflected by low conjugated bilirubin or in patients where an irinotecan dose of >180 mg/m^2 per administration is planned [III, C].**	100%
2: Staging and risk assessment	
2a. Staging is carried out primarily with imaging techniques, such as a contrast-enhanced CT of the thorax, abdomen and pelvis[14] [IV, A].	100%
2b. A liver MRI scan is recommended to characterise non-typical liver lesions on CT scans or when liver metastases seem resectable or potentially resectable[28] [IV, A].	100%
2c. An FDG-PET scan can be useful, particularly in patients with increased tumour markers without evidence of metastatic disease, or to define the extent of metastatic disease on potentially resectable metastases[14] [IV, B].	100%
2d. Resection of an asymptomatic primary tumour in patients with unresectable metastatic disease cannot be recommended as standard of care[29,30] [I, D].	100%
3: Management of resectable/potentially resectable disease	
Treatment of potentially resectable mCRC	
3a. In patients with resectable metastases and with favourable prognostic criteria and a good surgical approach, perioperative systemic treatment may not be needed [III, B].	100%
3b. In patients with resectable metastases, the use of perioperative oxaliplatin-based chemotherapy is recommended where the prognostic situation is unclear [II, B].	100%
3c. Anti-EGFR mAbs in left-sided *RAS* wt patients should be used as conversion therapy, when complete resection is the aim [II, A].	100%
3d. In patients with right-sided and *RAS* mutant disease, FOLFOXIRI-bevacizumab and, to a lesser extent, a cytotoxic doublet-bevacizumab should be considered the best choice depending on patients' ability to tolerate triplet chemotherapy [II, A].	100%
3e. **Patients with metastases progressing on first-line chemotherapy should be assessed for resection** after second-line treatment **benefit**. Intra-arterial chemotherapy **may be a second-line** option not only to achieve a response but also liver resection [III, C].	100%
3f. In case of a peritoneal metastasis only, complete cytoreductive surgery should be carried out [II, A]. The addition of HIPEC can be considered as an experimental procedure, still to be validated in clinical trials. Therefore, its use cannot be recommended outside of this setting [II, D].	100%
Intent and choice of local treatment	
3g. Treatment approaches for all patients with mCRC should be discussed within an MDT of experts (especially in patients amenable to LT) who meet regularly to review OMD cases [V, A].	100%
3h. Local treatment **may** be used as a primary or metastasis-specific treatment or following systemic therapy, as a consolidation strategy [III, C].	100%
3i. Frequent radiological re-evaluations of the potential applicability of surgery or other LT techniques should be carried out, generally every 8-12 weeks [IV, A].	100%
Local ablation treatment	
3j. In patients with unresectable CRLMs only, or OMD in the liver, TA can be considered for small metastases [III, B].	100%
3k. TA is a valid treatment option for recurrent disease after surgical resection for small CRLMs[31-33] [II, B].	100%
3l. In patients with lung-only metastases or OMD including lung lesions, TA may be considered along with resection, according to tumour size, number, location, the extent of lung parenchyma loss, comorbidity or other factors[34-37] [III, B].	100%
3m. SBRT is a treatment option, although it is yet unclear which patients benefit most[38,39] [III, B].	100%
Intra-arterial therapies	
3n. TACE, TARE/SIRT and HAIC may be considered as treatment options with non-curative intent, **if available in expert centres [**III, **C]. Patient participation in related clinical trials should be encouraged.**	100%
3o. SIRT, HAIC and chemoembolisation of CRLMs in earlier treatment lines may be interesting as 'consolidation treatment' but should be limited to clinical trials [V, D].	100%

Continued

Table 1. Continued

Recommendations	Acceptability consensus
4: Management of advanced and metastatic disease without potential for conversion	
First-line therapy	
4a. Determining the *RAS* mutational status on a tumour biopsy [I, A] (or through a liquid biopsy in case no tumour sample is available [II, B]) is mandatory to guide the best treatment decision.[40-43]	100%
4b. Delivering a biological therapy in combination with chemotherapy in the first-line setting is recommended, unless contraindicated[16,43-50] [I, A].	100%
4c. In the majority of patients, first-line treatment will consist of a doublet of chemotherapy (FOLFOX, FOLFIRI, CAPOX) that can be combined with an anti-VEGF or anti-EGFR mAb [I, B; for cetuximab-FOLFIRI ESMO-Magnitude of Clinical Benefit Scale (ESMO-MCBS) v1.1 score: 4; panitumumab-FOLFOX4 ESMO-MCBS v1.1 score: 4; panitumumab—modified FOLFOX6 ESMO-MCBS v1.1 score: 3].	100%
4d. In *RAS* wt and *BRAF* wt left-sided tumours, doublet chemotherapy plus an anti-EGFR mAb is the preferred option[51,52] [I, A]. Due to increased side-effects and lack of efficacy, combination of cetuximab with capecitabine[47] or bolus 5-FU-based chemotherapy[53] is not recommended [I, E].	100%
4e. In *RAS* wt right-sided tumours, chemotherapy ± bevacizumab is the preferred option [II, B], although in cases in which a higher response is needed for conversion therapy, a doublet with cetuximab or panitumumab can be used [II, C].	100%
4f. Anti-EGFR mAbs can be combined with the doublets FOLFOX or FOLFIRI [I, A; panitumumab-FOLFOX4 ESMO-MCBS v1.1 score: 4; panitumumab-modified FOLFOX6 ESMO-MCBS v1.1 score: 3; for cetuximab-FOLFIRI ESMO-MCBS v1.1 score: 4].	100%
4g. Bevacizumab can be combined with single fluoropyrimidines, irinotecan- or oxaliplatin-based doublet of chemotherapy (FOLFOX, CAPOX, FOLFIRI) or triplets (FOLFOXIRI) [I, B].	100%
4h. Combining anti-VEGF plus anti-EGFR mAbs is not recommended [I, E].	100%
4i. A triplet with FOLFOXIRI plus bevacizumab could also be an option for selective patients with good PS and without comorbidities [I, B; ESMO-MCBS v1.1 score: 2]. Triplets including FOLFOXIRI should not be used in patients >75 years old, with PS2 or in patients with significant comorbidities [IV, E].	100%
4j. In selected cases, when downstaging is the objective or in right-sided colon cancer with *BRAF* V600E mutations, a triplet (FOLFOXIRI), which can be combined with bevacizumab, should be considered, but a doublet plus bevacizumab could provide similar outcomes[54] [II, B].	100%
4k. Triplets with FOLFOXIRI and anti-EGFR mAbs are not **currently** recommended [I, D].	100%
4l. In patients with comorbidities, older age or with metastatic disease not amenable to a curative treatment strategy and no significant disease-related symptoms, monotherapy with a fluoropyrimidine ± bevacizumab can be used [I, B]. In frail or elderly patients unable to tolerate chemotherapy, whose tumours are left-sided and *RAS* wt, monotherapy with anti-EGFR mAbs can be considered [**III**, C].	100%
4m. In patients **unable to tolerate** cardiotoxicity and/or hand-foot syndrome on 5-FU or capecitabine-based chemotherapy, S-1 may be used as an alternative [III, B].	100%
4n. Patients should receive all available treatments during the course of the disease [I, B].	100%
4o. In dMMR/MSI-H mCRC patients, the ICI pembrolizumab has demonstrated benefit over standard chemotherapy and targeted agents in the first-line setting and it is recommended as standard of care [I, A; ESMO-MCBS v1.1 score: 4; ESCAT: I-A].	100%
Maintenance therapy	
4p. After first-line therapy with chemotherapy based on oxaliplatin—bevacizumab, maintenance therapy with a fluoropyrimidine and bevacizumab could be considered in non-progressive patients after at least 4 months of treatment[55] [I, B].	100%
4q. After first-line therapy with chemotherapy based on oxaliplatin plus anti-EGFR mAbs, maintenance therapy with a fluoropyrimidine plus anti-EGFR mAbs could be considered in non-progressive patients[56,57] [II, B].	100%
4r. When FOLFIRI is used in first-line treatment, **it can be continued until disease progression if well tolerated [V, B].**	100%
4s. Reintroduction of an initial successful induction therapy should be done after progressive disease while on **durable** maintenance therapy [III, B].	100%
Second-line treatment	
4t. In patients treated first line with oxaliplatin-based therapy, second-line treatment with irinotecan-based therapy or monotherapy is recommended. On the contrary, for those patients treated with irinotecan-based therapy first line could receive oxaliplatin-based therapy (FOLFOX or CAPOX) second line, if there are no contraindications [II, A].	100%
4u. In *RAS* wt patients not previously treated with an anti-EGFR mAb, treatment with chemotherapy (FOLFIRI or irinotecan) and cetuximab or panitumumab could be considered for left-sided colon tumours[57,58] [II, C]. For right-sided tumours, second-line therapy with an antiangiogenic combined with chemotherapy is recommended [II, B].	100%
4v. In patients previously treated with irinotecan-fluoropyrimidine-based chemotherapy alone, a combination of bevacizumab-FOLFOX is recommended[59] [I, A].	100%
4w. Second-line treatment with an antiangiogenic combined with chemotherapy, regardless of whether first-line treatment included bevacizumab or not, should be used, independently of the *RAS* mutational status and the PTL[60] [I, A].	100%
4x. Bevacizumab can be combined with a fluoropyrimidine-doublet with oxaliplatin or irinotecan, depending on the first-line chemotherapy backbone delivered [I, A; ESMO-MCBS v1.1 score: 1].	100%
4y. Aflibercept or ramucirumab in combination with FOLFIRI could be used as an alternative to bevacizumab with FOLFIRI in patients progressing on first-line treatment with oxaliplatin-based chemotherapy[61,62] [I, A; ESMO-MCBS v1.1 score: 1].	100%
4z. For pre-treated mCRC patients with BRAF V600E-mutated tumours, encorafenib—cetuximab is recommended as the best option in second line[63] [I, A; ESMO-MCBS v1.1 score: 4; ESCAT: I-A]. **The addition of binimetinib may be an option, if available.**[19]	100%
4aa. For dMMR/MSI-H tumours progressing after first-line chemotherapy, ipilimumab—nivolumab is recommended[64,65] [III, B; ESMO-MCBS v1.1 score: 3]. **Nivolumab[66] [III, C; ESMO-MCBS v1.1 score: 3] or pembrolizumab monotherapy is an option[67] [III, C; ESMO-MCBS v1.1 score: 3].**	100%

Continued

Table 1. Continued

Recommendations	Acceptability consensus
Third- and further-line treatment	
4bb. Reintroduction of the initial induction therapy can be considered after second-line therapy, as long as the patient did not progress during the induction course of first-line chemotherapy [III, B].	100%
4cc. Regorafenib is recommended in patients pre-treated with fluoropyrimidines, oxaliplatin, irinotecan and biologics, if available, or in earlier lines of therapy following oxaliplatin and irinotecan regimen failure, depending on local approvals[68,69] [I, A, ESMO-MCBS v1.1 score: 1].	100%
4dd. Trifluridine—tipiracil **plus or minus bevacizumab** is recommended in patients pre-treated with fluoropyrimidines, oxaliplatin, irinotecan and biologics, if available, or in earlier lines of therapy following oxaliplatin and irinotecan regimen failure, depending on local approvals[70–72] [I, A].	100%
4ee. For *BRAF* V600E-mutated, pre-treated mCRC patients, encorafenib—cetuximab is recommended as the best option in third line [I, A; ESMO-MCBS v1.1 score: 4; ESCAT: I-A]. **The addition of binimetinib may be an option, if available.**[19]	100%
4ff. In *RAS* wt and *BRAF* wt patients not previously treated with anti-EGFR antibodies, cetuximab **or** panitumumab are recommended as single agents[73–75] [I, A; panitumumab ESMO-MCBS v1.1 score: 3].	100%
4gg. In irinotecan-refractory patients, cetuximab—irinotecan is recommended over cetuximab alone[73] [II, B].	100%
4hh. Administering an alternative anti-EGFR antibody, if a patient is refractory to one of the other anti-EGFR antibodies, is not recommended [I, E].	100%
4ii. In patients maintaining *RAS* wt status, rechallenge with anti-EGFR mAbs may be an option in selected patients[76,77] [III, C].	100%
4jj. In HER2-positive patients with mCRC, treatment with HER2 dual blockade is optionally recommended, especially in *RAS* wt tumours [III, C; ESCAT: II-B].	100%
4kk. **Fruquintinib is an additional option in patients pre-treated with fluoropyrimidines, oxaliplatin, irinotecan and biologics**[78,79] **[I, B].**	100%
5: Follow-up, long-term implications and survivorship	
5a. For patients receiving active treatment, radiological evaluation should be carried out **at least** every **12 weeks**, including (in most cases) a CT scan or MRI **scan**, as well as the measurement of **tumour marker levels** [IV, B].	100%
5b. Patients with a radically resected metastatic disease with potential for cure merit more intense monitoring initially with radiological assessment with CT (or MRI) and measurement of CEA levels every 3 months during the first 2 years and every 6 months thereafter [I, A].	100%

5-FU, fluorouracil; CAPOX, capecitabine -oxaliplatin; CEA, carcinoembryonic antigen; CRLM, colorectal liver metastasis; CT, computed tomography; dMMR, defective mismatch repair; DPD, dihydropyrimidine dehydrogenase; EGFR, epidermal growth factor receptor; ESCAT, ESMO Scale for Clinical Actionability of Molecular Targets; ESMO-MCBS, ESMO-Magnitude of Clinical Benefit Scale; FDG-PET, ^{18}F fluorodeoxyglucose-positron emission tomography; FISH, fluorescence in situ hybridisation; FOLFIRI, 5-FU—leucovorin—irinotecan; FOLFOX, 5-FU—LV—oxaliplatin; FOLFOXIRI, FOLFOX plus irinotecan; HAIC, hepatic arterial infusion chemotherapy; HER2, human epidermal growth factor receptor 2; HIPEC; hyperthermic intraperitoneal chemotherapy; ICI, immune checkpoint inhibitor; IHC, immunohistochemistry; LT, local treatment; mAbs, monoclonal antibodies; mCRC, metastatic colorectal cancer; MDT, multidisciplinary team of experts; MRI, magnetic resonance imaging; MSI, microsatellite instability; MSI-H, microsatellite instability-high; *NTRK*, neurotrophin receptor tyrosine kinase; OMD, oligometastatic disease; PS, performance status; PTL, primary tumour location; SBRT, stereotactic body radiotherapy; SIRT, selective internal radiotherapy; TA, thermal ablation; TACE, transarterial chemoembolisation; TARE, transarterial radioembolisation; HR, hazard ratio; VEGF, vascular endothelial growth factor; wt, wild-type.

Also, where *HER2* testing is not reimbursed consideration should be given to referring patients to centres conducting clinical trials. In some Asian countries *HER2* testing is carried out at the same time as *RAS*, *BRAF* and mismatch repair deficiency (dMMR)/microsatellite instability (MSI) testing to minimise the loss of tumour specimens. Although, it should be noted that in some Asian countries *HER2* testing is only carried out in patients with *RAS* wt disease for the same reason.

Furthermore, a recent Asian phase II study has shown that circulating tumour cell DNA (ctDNA) genotyping can identify patients who can benefit from dual human epidermal growth factor receptor 2 (HER2) blockade as well as monitor treatment response. These results warrant the further investigation of ctDNA genotyping for patients with *HER2*-amplified mCRC in clinical trials.[81]

The representatives of 9 of the 10 Asian countries, however, did not consider 'recommendation 1k' acceptable in the pre-meeting survey (Supplementary Table S2, available at https://doi.org/10.1016/j.esmoop.2023.101558) on the basis that the incidence of dihydropyrimidine dehydrogenase (DPD) deficiency is estimated to be very low in Asian populations compared with non-Asian populations. A Japanese study investigated the incidence of DPD deficiency in 1362 Asian colon cancer patients who were enrolled in the JOIN[82] and ACHIEVE[83] adjuvant chemotherapy trials and suggested that the incidence of DPD deficiency for these patients was in the region of 0.6%, with no clear association observed between DPD deficiency and safety.[84] In addition, DPD deficiency was not detected by analysing DPD full-length RNA polymorphisms in peripheral blood mononuclear cells in 67 Taiwanese patients using multiplex nested reverse transcription-polymerase chain reaction (RT-PCR) and non-isotopic RNase cleavage assays (NIRCA).[85] DPD deficiency is also reported not to be common in Korea.[86] Thus, due to the low incidence of DPD deficiency in Asian patients, DPD genotyping and phenotyping is not carried out in routine daily practice in Asia, but is recommended for patients, who experience severe 5-fluorouracil (5-FU) toxicity during and after their first cycle of chemotherapy. 'Recommendation 1k' was therefore revised from the original ESMO recommendation (Supplementary Table S2, available at https://doi.org/10.1016/j.esmoop.2023.101558), to be consistent with the Pan-Asian adaptation of the ESMO Clinical Practice Guidelines for the diagnosis treatment and follow-up of patients with localised

colon cancer,[27] as per the bold text below, and the GoR revised to C and a new statement added.

1k. **Depending on the anticipated genetic profile of a specific Asian patient population**, DPD genotyping or phenotyping **may be considered** before initiating fluoropyrimidine-based therapy [III, **C**]. **DPD genotyping or phenotyping should be implemented in patients who experience severe fluoropyrimidine toxicity [V; consensus = 100%]** (Table 1).

The experts from JSMO also proposed the addition of a new recommendation, 'recommendation 1l' below and Table 1, based on data from several Asian studies regarding irinotecan toxicity.[87-93] Genetic variations within the UDP glucuronosyltransferase 1 family, polypeptide A1 (*UGT1A1*) gene have been associated with the development of certain drug toxicities, with the *UGT1A1*6* variant, common in Asian populations.[93] *UGT1A1* gene polymorphisms are predictive of irinotecan-related side-effects, including diarrhoea, neutropaenia and vomiting. A systematic review and meta-analysis has shown the increased risk of severe neutropaenia in cancer patients with *UGT1A1*6* polymorphisms.[94]

1l. ***UGT1A1* genotyping remains an option and it is recommended that it is carried out in patients with a suspicion of UGT1A1 deficiency as reflected by low conjugated bilirubin or in patients where an irinotecan dose of >180 mg/m^2 per administration is planned [III, C; consensus = 100%]**.

It was also recommended that depending on the prevalence of *UGT1A1* polymorphisms per country, a lower irinotecan threshold dose for *UGT1A1* genotyping may be used.

Supplementary Table S3, available at https://doi.org/10.1016/j.esmoop.2023.101558 describes the biomarkers and molecular targets for precision medicine and the corresponding ESMO Scale for Clinical Actionability of molecular Targets (ESCAT) scores.

2. Staging and risk assessment—recommendations 2a-d. The Pan-Asian panel of experts agreed with and accepted completely (**100% consensus**) the original ESMO recommendations, 'recommendations 2a-d' Supplementary Table S2, available at https://doi.org/10.1016/j.esmoop.2023.101558 and Table 1.

3. Management of resectable/potentially resectable disease—recommendations 3a–f

Treatment of patients with potentially resectable mCRC. The Pan-Asian panel of experts agreed with and accepted completely (**100% consensus**) the original ESMO recommendations, 'recommendations 3a-d and 3f' (Table 1).

There was, however, much discussion about the precise meaning of the ESMO 'recommendation 3e' below (and Supplementary Table S2, available at https://doi.org/10.1016/j.esmoop.2023.101558) which states that:

3e. *Patients unresponsive to first-line chemotherapy should not be denied resection or ablation of their metastases since the outcome of resected patients after second-line treatment could be also favourable. Intra-arterial chemotherapy could be an option in such patients, not only to recover a response but also to achieve liver resection [III, C].*

It was agreed by the experts that patients unresponsive to first-line therapy should be assessed for resection after a second-line treatment benefit is observed in the absence of contraindications. Thus, 'recommendation 3e' was reworded as per the bold text, below and Table 1.

3e. **Patients with metastases progressing on first-line chemotherapy should be assessed for resection** after second-line treatment **benefit**. Intra-arterial chemotherapy **may be used as a second-line** option not only to achieve a response but also liver resection [III, C; **consensus = 100%]**.

Intent and choice of local treatment. The Pan-Asian panel of experts agreed with and accepted completely (**100% consensus**) the original ESMO recommendations, 'recommendations 3g and 3i' (Table 1), but discussions at the hybrid virtual/face-to-face meeting led to the rewording of the original 'recommendation 3h'.

The original 'recommendation 3h' below was revised and shortened (as per the bold text) for better understanding from:

3h. *Local treatment can be used as a primary or metastasis-specific treatment to halt further dissemination, and/or following systemic therapy as a consolidation treatment, to delay or pause further treatment [III, C].*

to read as follows:

3h. Local treatment **may** be used as a primary or metastasis-specific treatment **or** following systemic therapy as a consolidation **strategy** [III, C; **consensus = 100%**] (Table 1).

Local ablation treatment. The Pan-Asian panel of experts agreed with and accepted completely (**100% consensus**) the original ESMO recommendations, 'recommendations 3j—m' (Table 1). An algorithm summarising the options for local ablation treatment is presented in Figure 1.

Intra-arterial therapies. The Pan-Asian panel of experts revised 'recommendation 3n' below to more accurately reflect the situation in their countries. In Korea and Taiwan intra-arterial therapies are only used within the remit of a clinical trial, whilst in Japan they are not commonly used at all. The feeling amongst the experts was that hepatic arterial infusion chemotherapy (HAIC) in particular was limited by a lack of expertise. The experts from TSCO considered that the evidence to support the use of transarterial chemoembolisation (TACE) was inadequate. Thus, the consensus was that such procedures should be limited to expert centres or clinical trials. The wording of the original 'recommendation 3n' below:

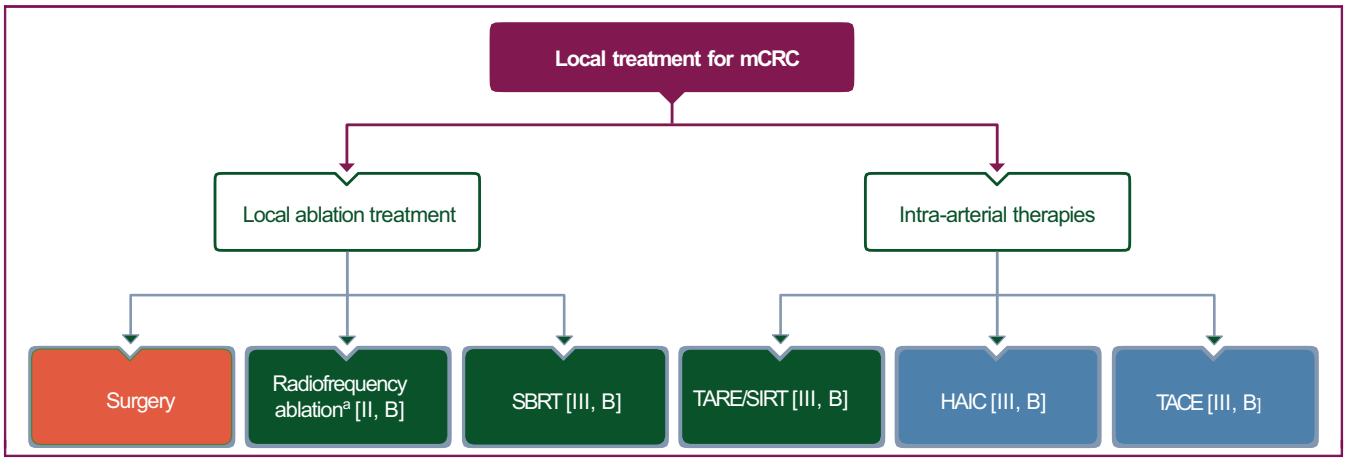

Figure 1. Local treatment of CRC metastases.
Purple box: general categories or stratification; orange box: surgery; dark green boxes: radiotherapy; blue boxes: systemic anticancer therapy; white boxes: other aspects of management.
HAIC, hepatic arterial infusion chemotherapy; mCRC, metastatic colorectal cancer; SBRT, stereotactic body radiotherapy; SIRT, selective internal radiotherapy; TACE, transarterial chemoembolisation; TARE, transarterial radioembolisation.
[a]In patients with unresectable colorectal liver metastases only, or oligometastatic disease (OMD) in the liver, thermal ablation (TA) can be considered for small metastases [III, B]. In patients with lung-only metastases or OMD including lung lesions, TA may be considered along with resection, according to tumour size, number, location, the extent of lung parenchyma loss, comorbidity, or other factors [III, B].

3n. *TACE, TARE/SIRT and HAIC may be also considered as treatment options with non-curative intent [III, B],*

was revised to read:

3n. TACE, transarterial radioembolisation (TARE)/selective internal radiotherapy (SIRT) and HAIC may be considered as treatment options with non-curative intent, **if available in expert centres [**III, **C; consensus = 100%]. Patient participation in related clinical trials should be encouraged.**

The GoR was revised from B to **C**.

The Pan-Asian panel of experts agreed with and accepted completely (**100% consensus**) the ESMO 'recommendation 3o' (Table 1) in the pre-meeting survey without change.

The options for intra-arterial therapy are summarised in Figure 1.

4. Management of advanced and metastatic disease without potential for conversion—recommendations 4a–jj

First-line therapy. The Pan-Asian panel of experts agreed with and accepted completely (**100% consensus**) the original ESMO recommendations, 'recommendations 4a-d' and 4f-j, (Table 1).

The Asian experts also accepted the original 'recommendation 4e' without change (Table 1), after discussion of whether there was evidence to support the benefit of the addition of anti-epidermal growth factor receptor monoclonal antibody (anti-EGFR mAb) therapy (either cetuximab or panitumumab) to doublet chemotherapy in patients with right-sided *RAS* wt primary tumours. Data from the Japanese PARADIGM trial (NCT02394795), the first prospective trial to test the superiority of panitumumab versus bevacizumab in combination with standard doublet (mFOLFOX6) first-line chemotherapy for patients with *RAS* wt mCRC and left-sided primary tumours, showed panitumumab to statistically significantly improve overall survival and improve response rate and R0 resection rate compared with bevacizumab when used in combination with mFOLFOX6.[95] The statistically significant overall survival benefit and improved response rate and R0 resection rates was retained in the full analysis population, consistent with the data that support the use of anti-EGFR mAb therapy in combination with chemotherapy first line in patients with *RAS* wt/*BRAF* wt left-sided primary tumours. Although, additional data showed that patients with right-sided tumours did not derive an overall survival benefit when treated with panitumumab in combination with chemotherapy, the R0 resection rate for patients with right-sided tumours was similar for patients who received either panitumumab or bevacizumab.[96] More recently, a biomarker study of PARADIGM trial patients has shown that overall survival tended to be longer for selected patients with no gene alterations treated with panitumumab than for those treated with bevacizumab, irrespective of tumour sidedness.[97] This suggests that selection of patients with *RAS* wt mCRC using ctDNA analysis may further refine the selection of patients for treatment with panitumumab rather than bevacizumab in the first-line treatment setting.

There was considerable discussion around 'recommendation 4k', however, with the available clinical data presenting conflicting results regarding the addition of anti-EGFR mAbs to triplet FOLFOXIRI (FOLFOX plus irinotecan) therapy first line. FOLFOXIRI, combined with bevacizumab[54] or panitumumab,[98] has been shown to be superior when compared with doublet combinations in patients with *RAS* wt mCRC. The Japanese randomised phase II DEEPER trial (NCT02515734) of FOLFOXIRI plus cetuximab versus FOLFOXIRI plus bevacizumab first line in patients with *RAS* wt

mCRC showed FOLFOXIRI plus cetuximab to be significantly superior to FOLFOXIRI plus bevacizumab in terms of depth of response (DpR), the primary endpoint.[99] There is no phase III evidence, however, to support the use of anti-EGFR mAbs in combination with triplet chemotherapy as demonstrated by the European TRIPLETE trial which failed to show a benefit for FOLFOXIRI plus panitumumab versus FOLFOX plus panitumumab in terms of early tumour shrinkage and DpR.[100] Thus, the word 'currently' was added to the original recommendation 4k as per the bold text below, and also Table 1.

4k. Triplets with FOLFOXIRI and anti-EGFR mAbs are not **currently** recommended [I, D; **consensus 100%**].

The Asian experts also accepted 'recommendation 4l' (Table 1) unchanged (**100% consensus**), supported by data from the Japanese phase II OGSG 1602 study (UMIN000024528) of panitumumab monotherapy in chemotherapy-naive frail/elderly patients with unresectable *RAS* wt metastatic/advanced CRC.[101] The LoE however, was revised to **III**, C (Table 1).

The Asian experts were did not agree with the wording of the original 'recommendation 4m' and thought that the wording should reflect attempts at dose modification. The oral fluoropyrimidine S-1, developed as a prodrug of 5-FU, is frequently used in Asia and can be used when i.v. 5-FU or capecitabine-based chemotherapy cannot be tolerated, due to cardiotoxicity and/or hand-foot syndrome.[102]

Thus, the original wording of 'recommendation 4m' below:

4m. *In patients presenting with cardiotoxicity and/or hand-foot syndrome on 5-FU or capecitabine-based chemotherapy, S-1 may be used as an alternative [III, B],*

was revised to read:

4m. In patients **unable to tolerate** cardiotoxicity and/or hand-foot syndrome on 5-FU or capecitabine-based chemotherapy, S-1 may be used as an alternative [III, B; **consensus = 100%**].

The Asian experts also accepted 'recommendations 4n and 4o' unchanged (Table 1) (**100% consensus**) with the observation with regard to 'recommendation 4o', in patients with dMMR/MSI disease, that although the overall survival of the patients receiving the immune checkpoint inhibitor (ICI) pembrolizumab was not significantly longer in the KEYNOTE-177 study (probably because of the 60% cross-over), it was superior, in those patients receiving pembrolizumab. The primary endpoint prolongation of progression-free survival was met.[103,104] As a consequence the consensus was that the ICI pembrolizumab can be recommended as a standard of care, for the treatment of patients with dMMR/MSI mCRC in the first-line setting.

A summary of the first-line treatment options for the management of patients with stage IV unresectable mCRC is presented in Figure 2.

Maintenance therapy. Consideration of maintenance therapy is generally applicable to those patients who are not amenable to surgery or local therapy and involves a de-escalation in the intensity of their systemic treatment with a concomitant improvement in treatment-related side-effects.

The Asian experts accepted completely (**100% consensus**) 'recommendations 4p and 4q' relating to maintenance therapy, without change (Table 1), in the pre-meeting survey.

The Asian experts thought the wording of 'recommendations 4r and 4s' was unclear (Supplementary Table S2, available at https://doi.org/10.1016/j.esmoop.2023.101558), however, and they were revised accordingly as indicated by the bold text below and Table 1.

4r. When FOLFIRI is used in first-line treatment, **it can be continued until disease progression if well tolerated** [V, B; **consensus = 100%**].

4s. Reintroduction of an initial successful induction therapy should be done after progressive disease while on **durable** maintenance therapy [III, B; **consensus = 100%**].

A summary of the maintenance treatment options according to prior therapy are summarised in Figure 3.

Second-line therapy. The Asian experts accepted 'recommendations 4t-y' relating to second-line therapy, unchanged (Table 1) (**100% consensus**), and after discussion, 'recommendations 4u, 4v and 4w'. A modification was made to 'recommendation 4z' below and Table 1, however, as per the bold text, based on data from the BEACON trial (NCT02928224),[19] at the request of the JSMO experts, as encorafenib—cetuximab plus or minus binimetinib, is reimbursed in Japan for patients with ECOG performance status of 1, >3 metastatic sites, high serum creatinine protein levels (>1 mg/dL), or no history of primary tumour resection.

4z. For pre-treated mCRC patients with *BRAF* V600E-mutated tumours, encorafenib—cetuximab is recommended as the best option in second line[63] [I, A; ESMO-MCBS v1.1 score: 4; ESCAT: I-A]. **The addition of binimetinib may be an option, if available (consensus = 100%)**.

Recommendation 4aa was discussed and an additional statement added to the recommendation, as per the bold text below and Table 1, to include the option to use nivolumab or pembrolizumab monotherapy second line for patients with dMMR/MSI-H mCRC.

4aa. For dMMR/MSI-H tumours progressing after first-line chemotherapy, ipilimumab—nivolumab is recommended[65] [III, B; ESMO-MCBS v1.1 score 3]. **Nivolumab[66] [III, C; ESMO-MCBS v1.1 score: 3; consensus = 100%] or pembrolizumab monotherapy is an option[67] [III, C; ESMO-MCBS v1.1 score: 3; consensus = 100%]**.

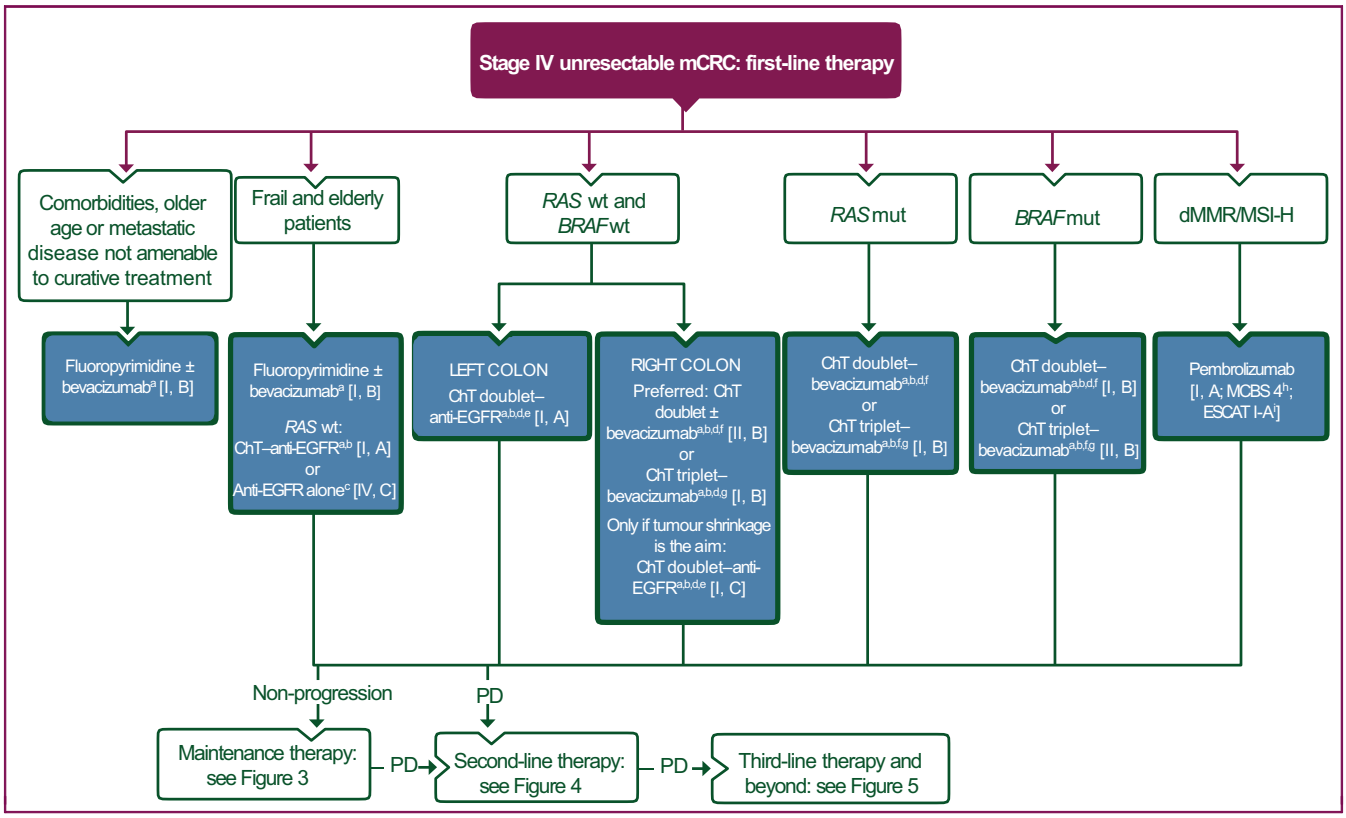

Figure 2. Management of stage IV unresectable mCRC in first-line therapy.
Purple box: general categories or stratification; blue boxes: systemic anticancer therapy; white boxes: other aspects of management.
5-FU, 5-fluorouracil; ChT, chemotherapy; dMMR, deficient mismatch repair; EGFR, epidermal growth factor receptor; EMA, European Medicines Agency; ESCAT, ESMO Scale for Clinical Actionability of Molecular Targets; MCBS, ESMO-Magnitude of Clinical Benefit Scale; FOLFOX, 5-FU—LV—oxaliplatin; FOLFOXIRI, FOLFOX plus irinotecan; mCRC, metastatic colorectal cancer; MSI-H, microsatellite instability-high; mut, mutant; PD, progressive disease; S-1, tegafur, 5-chloro-2, 4-dihydroxypyridine and potassium oxonate; wt, wild-type.
[a]In patients presenting with cardiotoxicity and/or hand-foot syndrome on 5-FU or capecitabine-based ChT, S-1 may be used as an alternative [III, B].
[b]Additional details on treatments and drug combinations can be found under 'Management of advanced and metastatic disease without potential conversion: first-line and second-line treatment'.
[c]In frail or elderly patients unable to tolerate ChT whose tumours are left-sided and *RAS* wt.
[d]Cetuximab—FOLFIRI ESMO-MCBS v1.1 score: 4; panitumumab—FOLFOX4 ESMO-MCBS v1.1 score: 4; panitumumab—modified FOLFOX6 ESMO-MCBS v1.1 score: 3.[h]
[e]Panitumumab—FOLFOX4 ESMO-MCBS v1.1 score: 4; panitumumab—modified FOLFOX6 ESMO-MCBS v1.1 score: 3; for cetuximab—FOLFIRI ESMO-MCBS v1.1 score: 4.[h]
[f]In a very selected population.
[g]A triplet with FOLFOXIRI plus bevacizumab is an option for selective patients with good performance status and without comorbidities [I, B; ESMO-MCBS v1.1 score: 2].[h]
[h]ESMO-MCBS v1.1 score for new therapy/indication approved by the EMA since 1 January 2016. The score has been calculated by the ESMO-MCBS Working Group and validated by the ESMO Guidelines Committee.
[i]ESCAT scores apply to genomic alterations only. These scores have been defined by the guideline authors and validated by the ESMO Translational Research and Precision Medicine Working Group.[105] See Supplementary Table S3, available at https://doi.org/10.1016/j.esmoop.2023.101558 for more information on ESCAT.

An algorithm of proposed second-line treatment options according to prior therapy and primary tumour mutation profile is presented in Figure 4.

Third-line and further therapy. Recently, the addition of bevacizumab to trifluridine—tipiracil has been shown to improve overall and progression-free survival, as well as objective response rate, when compared with trifluridine—tipiracil alone in the randomised phase III SUNLIGHT trial.[71] Also, cetuximab and panitumumab have both shown efficacy in this treatment setting in patients with *RAS* wt mCRC, as single agents.[73-75] In addition, treatment involving dual HER2 blockade using a combination of trastuzumab an anti-HER2 mAb and the tyrosine kinase inhibitor lapatinib has been shown to be effective in patients with *RAS* wt, HER2-positve, treatment-refractory mCRC.[22] An algorithm of proposed third-line and later-line treatment options according to the molecular profile of the primary tumour is presented in Figure 5.

The Asian experts accepted the original ESMO recommendations, 'recommendations 4bb, 4cc, 4gg and 4hh' without change (**100% consensus**) (Table 1) with the observation from the JSMO experts that the combination cetuximab—encorafenib—binimetinib[19,63] is also available in Japan in relation to 'recommendation 4ee'.

'Recommendation 4dd' was revised retrospectively as per the bold text below and Table 1, based on the data published from the SUNLIGHT trial.[71]

4dd. Trifluridine—tipiracil **plus or minus bevacizumab** is recommended in patients pre-treated with fluoropyrimidines, oxaliplatin, irinotecan and biologics, if available, or in earlier lines of therapy following oxaliplatin and irinotecan regimen failure, depending on local approvals [I, A; **consensus = 100%]**.

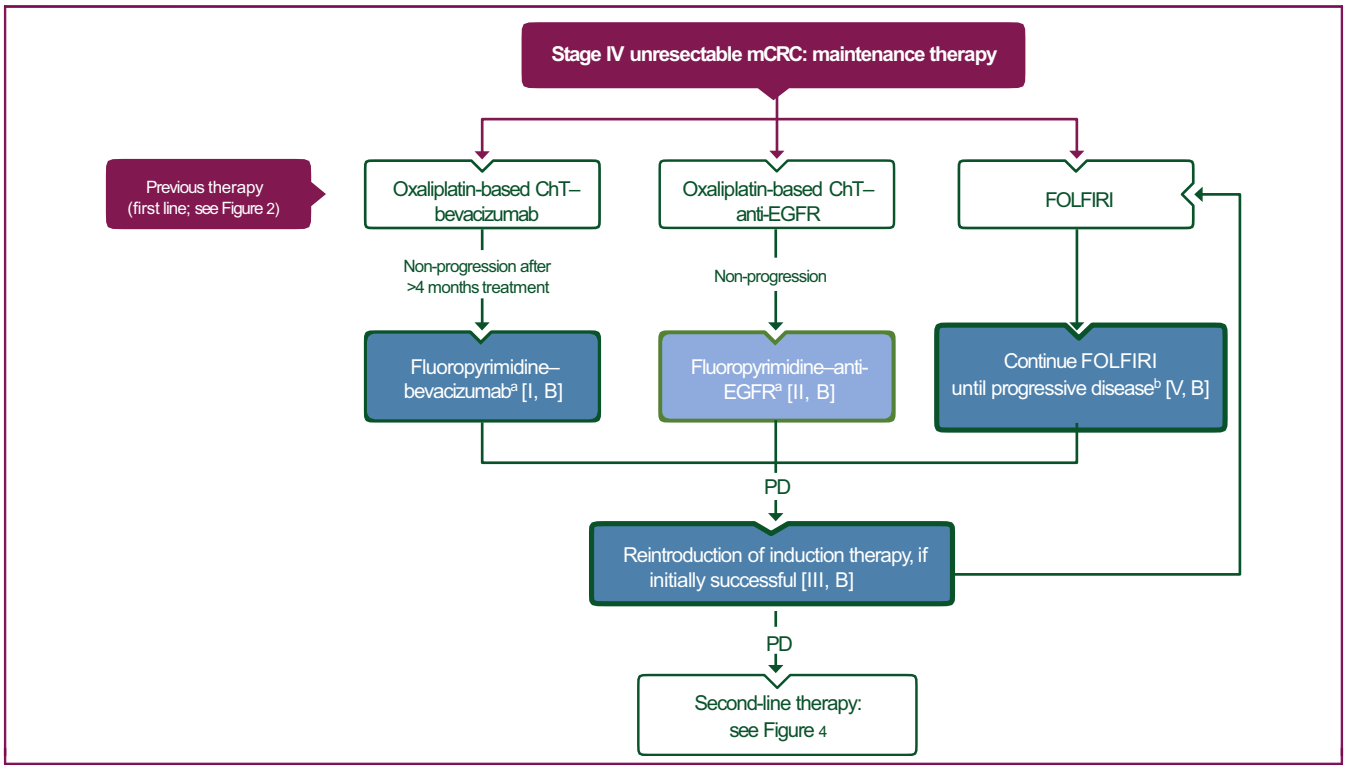

Figure 3. Management of stage IV unresectable mCRC with maintenance therapy.
Purple boxes: general categories or stratification; blue boxes and mauve box: systemic anticancer therapy; white boxes: other aspects of management.
5-FU, fluorouracil; ChT, chemotherapy; EGFR, epidermal growth factor receptor; FOLFIRI, folinic acid—fluorouracil—irinotecan; mCRC, metastatic colorectal cancer; PD, progressive disease; S-1, tegafur, 5-chloro-2, 4-dihydroxypyridine and potassium oxonate.
[a]In patients presenting with cardiotoxicity and/or hand-foot syndrome on 5-FU- or capecitabine-based ChT, S-1 may be used as an alternative [III, B].
[b]Due to the lack of a cumulative toxicity of FOLFIRI.

'Recommendation 4ee' was revised as per the bold text below and Table 1, as per 'recommendation 4z' above, based on data from the Beacon trial.[19]

4ee. For BRAF V600E-mutated, pre-treated mCRC patients, encorafenib—cetuximab is recommended as the best option in third line [I, A; ESMO-MCBS v1.1 score: 4; ESCAT: I-A]. **The addition of binimetinib may be an option, if available.**[19]

The Asian experts requested the minor modification to 'recommendation 4ff' with 'and' replaced by 'or' as per the bold text below and Table 1.

4ff. In *RAS* wt and *BRAF* wt patients not previously treated with the EGFR antibodies, cetuximab **or** panitumumab are recommended as single agents [I, A; panitumumab ESMO-MCBS v1.1 score: 3; **consensus = 100%**].

At the request of the experts from JSMO 'recommendation 4kk' was added below, and Table 1, for patients who had received prior fluoropyrimidine-, oxaliplatin- and irinotecan-based and anti-vascular endothelial growth factor (anti-VEGF) mAb therapy (and anti-EGFR-mAb therapy if *RAS* wt) based on data from the randomised Chinese FRESCO-1[79] and global FRESCO-2[78] trials of fruquintinib versus placebo plus or minus best supportive care, both of which reported a statistically significant improvement in overall survival.

4kk. **Fruquintinib is an additional option in patients pre-treated with fluoropyrimidines, oxaliplatin, irinotecan and biologics[78,79] [I, B; consensus = 100%].**

Also, it was noted that the phase II TRIUMPH study (UMIN000027887) of dual HER2 antibodies (pertuzumab plus trastuzumab) demonstrated promising activity in patients with HER2-positive mCRC, which led to the regulatory approval of this combination therapy in Japan.[81] Whilst, the durable response reported for the recent multicentre, open-label, phase II MOUNTAINEER trial (NCT03043313) in patients with HER2-positive *RAS* wt mCRC who had progressed on, or were intolerant to, fluoropyrimidine, oxaliplatin, irinotecan and anti-VEGF mAb therapy, treated with tucatinib and trastuzumab, means that this combination is likely to become a new treatment option for patients with chemotherapy-refractory HER2-positive *RAS* wt mCRC.[106]

5. Follow-up, long-term implications and survivorship—recommendations 5a—b. The Asian experts had concerns over the clarity of 'recommendation 5a' and the frequency of the proposed radiological evaluations. Several of the experts considered 8-12 weeks to be too frequent for patients receiving active treatment Thus, the original 'recommendation 5a' (Supplementary Table S2, available at https://doi.org/10.1016/j.esmoop.2023.101558) was revised, as per the bold text, to read as follows and Table 1.

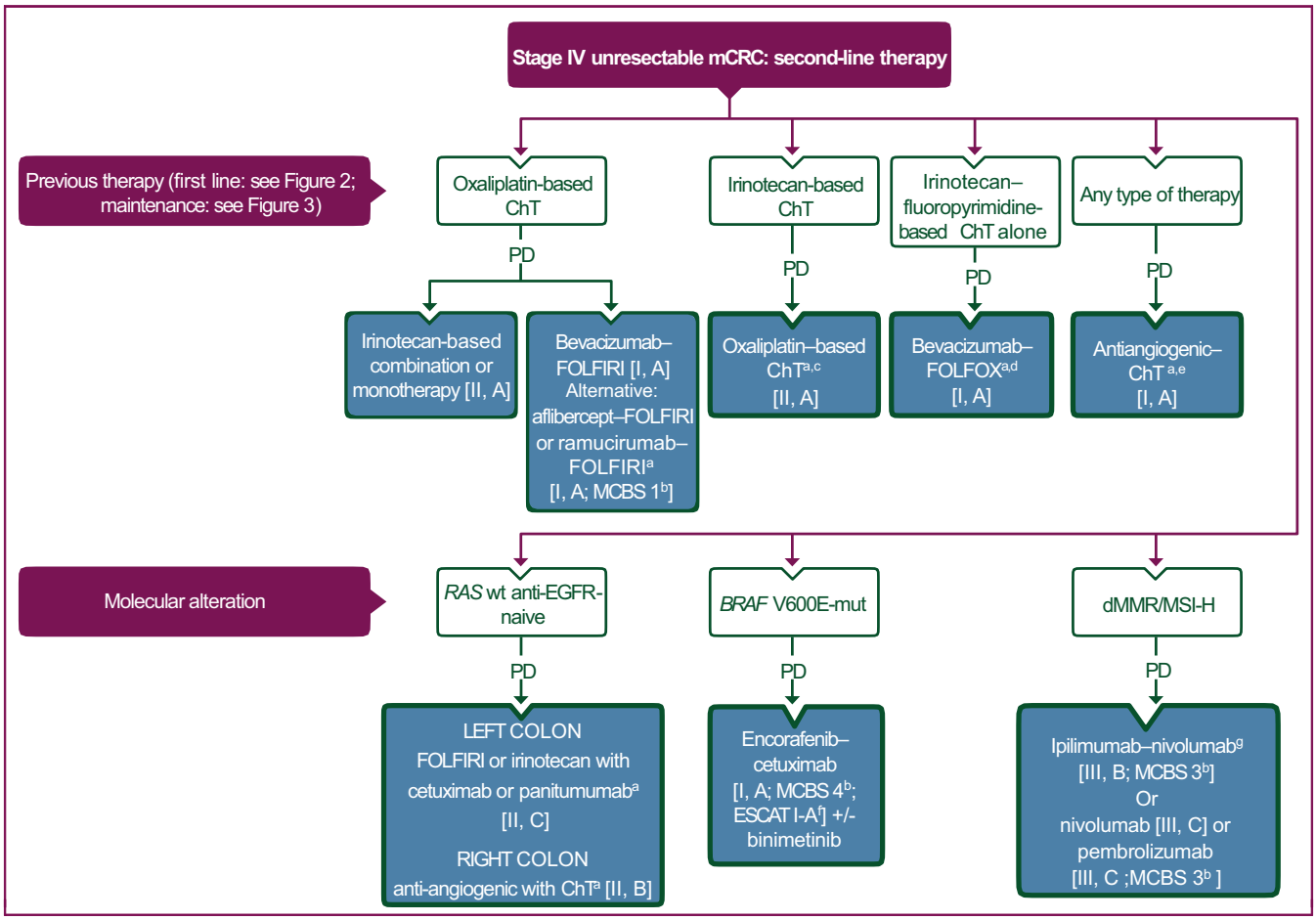

Figure 4. Management of stage IV unresectable mCRC in the second line.
Purple boxes: general categories or stratification; blue boxes: systemic anticancer therapy; white boxes: other aspects of management.
5-FU, fluorouracil; CAPOX, capecitabine—oxaliplatin; ChT, chemotherapy; EGFR, epidermal growth factor receptor; dMMR, deficient mismatch repair; ESCAT, ESMO Scale for Clinical Actionability of Molecular Targets; FOLFIRI, folinic acid—fluorouracil—irinotecan; FOLFOX, folinic acid—fluorouracil—oxaliplatin; MCBS, ESMO-Magnitude of Clinical Benefit Scale; mCRC, metastatic colorectal cancer; MSI-H, microsatellite instability-high; mut, mutant; PD, progressive disease; S-1, tegafur, 5-chloro-2, 4-dihydroxypyridine and potassium oxonate; wt, wild-type.
[a]In patients presenting with cardiotoxicity and/or hand-foot syndrome on 5-FU- or capecitabine-based ChT, S-1 may be used as an alternative [III, B].
[b]ESMO-MCBS v1.1 score for new therapy/indication approved by the EMA since 1 January 2016. The score has been calculated by the ESMO-MCBS Working Group and validated by the ESMO Guidelines Committee.
[c]FOLFOX or CAPOX, if no contraindications.
[d]Bevacizumab can be combined with a ChT doublet (a fluoropyrimidine with oxaliplatin or irinotecan, depending on the previous first-line ChT backbone) [I, A; ESMO-MCBS v1.1 score: 1].
[e]With or without previous first-line treatment with bevacizumab and independent of *RAS* mutational status and primary tumour location.
[f]ESCAT scores apply to genomic alterations only. These scores have been defined by the guideline authors and validated by the ESMO Translational Research and Precision Medicine Working Group.[105] See Supplementary Table S3, available at https://doi.org/10.1016/j.esmoop.2023.101558 for more information on ESCAT scores.
[g]Indicated for immunotherapy-naive patients.

5a. For patients receiving active treatment, radiological evaluation should be carried out **at least** every **12 weeks**, including (in most cases) a CT scan or MRI **scan**, as well as the measurement of **tumour marker levels** [IV, B; **consensus = 100%**].

The Asian experts accepted completely (**100% consensus**) the ESMO 'recommendation 5b' Table 1. A clinical assessment of the toxicities resulting from both systemic treatment and surgery should be conducted whenever possible together with an assessment of long-term survivors.

B. Applicability of the recommendations

Following the hybrid virtual/face-to-face working meeting, hosted by JSMO, the Pan-Asian panel of experts agreed with and accepted completely (**100% consensus**) the adapted ESMO guidelines listed in Table 1 above. The applicability of each of the guideline recommendations, however, is highly dependent on the drug and testing approvals for each Asian country and their reimbursement policies both of which differ markedly across the 10 countries represented.

The drug and treatment availability for the 10 Asian countries is summarised in Supplementary Table S5, available at https://doi.org/10.1016/j.esmoop.2023.101558 and outlined in the text below for each country individually and summarised individually for each country in Supplementary Tables S6-S15, available at https://doi.org/10.1016/j.esmoop.2023.101558.

Most notable are the striking differences between the individual countries in terms of their availability and

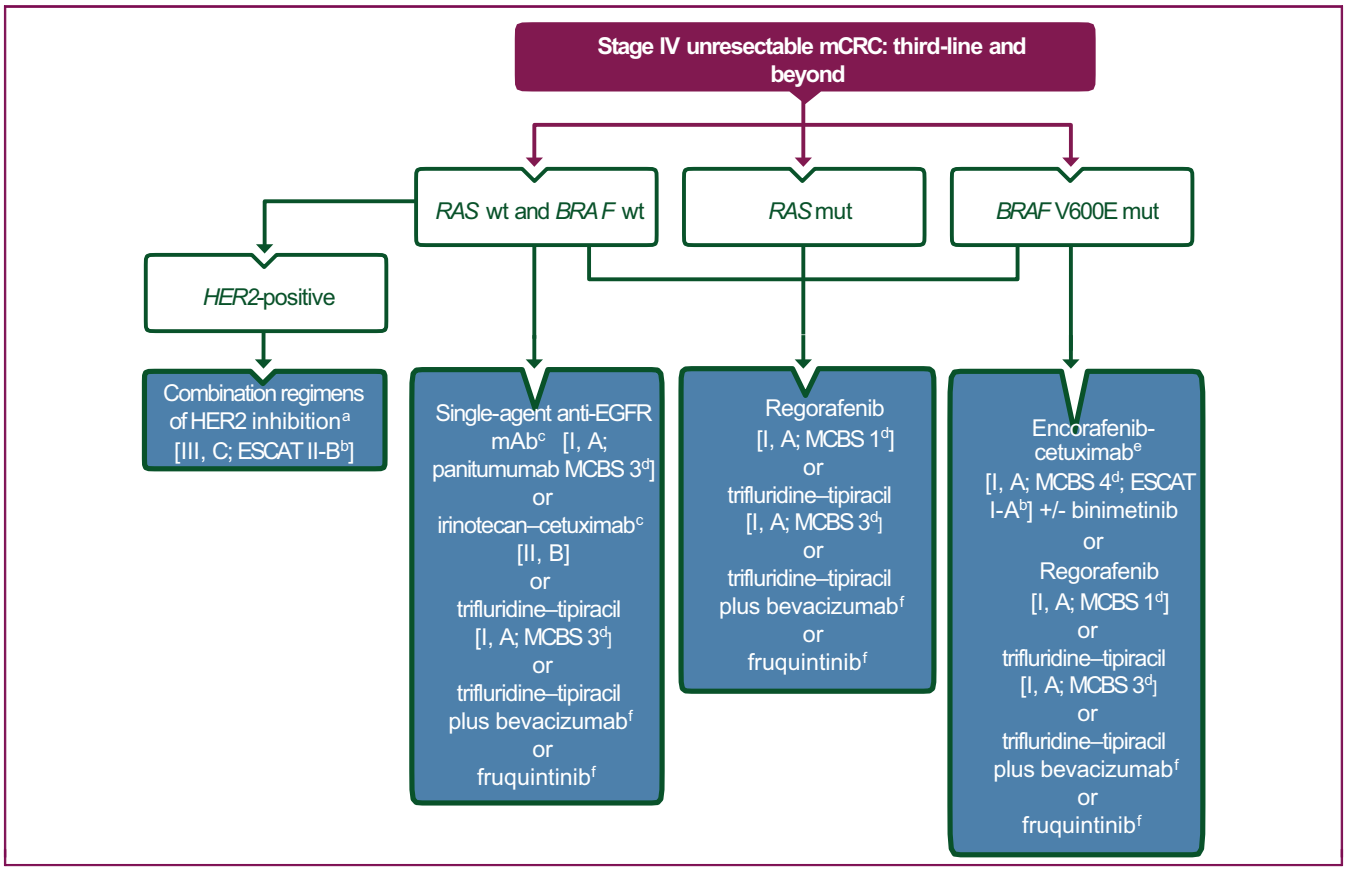

Figure 5. Management of stage IV unresectable mCRC in third- and later-line therapy.
Purple box: general categories or stratification; blue boxes: systemic anticancer therapy; white boxes: other aspects of management.
EGFR, epidermal growth factor receptor; EMA, European Medicines Agency; ESCAT, ESMO Scale for Clinical Actionability of Molecular Targets; FDA, Food and Drug Administration; HER2, human epidermal growth factor receptor 2; mAb, monoclonal antibody; MCBS, ESMO-Magnitude of Clinical Benefit Scale; mCRC, metastatic colorectal cancer; mut, mutant; PD, progressive disease; wt, wild-type.
[a]For a summary of recommended anti-HER2 regimens for mCRC see Supplementary Table S4, available at https://doi.org/10.1016/j.esmoop.2023.101558.
[b]ESCAT scores apply to genomic alterations only. These scores have been defined by the guideline authors and validated by the ESMO Translational Research and Precision Medicine Working Group.[105] See Supplementary Table S3, available at https://doi.org/10.1016/j.esmoop.2023.101558 for more information on ESCAT scores.
[c]In *RAS* wt patients not previously treated with anti-EGFR monoclonal antibodies.
[d]ESMO-MCBS v1.1 score for new therapy/indication approved by the EMA since 1 January 2016. The score has been calculated by the ESMO-MCBS Working Group and validated by the ESMO Guidelines Committee.
[e]Treatment for *BRAF*-mut patients if not used in the second line.
[f]Not EMA or FDA approved.

reimbursement policies with patients in Indonesia, Malaysia, The Philippines and Thailand having fewer approvals for testing and treatments, whilst also receiving very little reimbursement (Supplementary Tables S6-S9, available at https://doi.org/10.1016/j.esmoop.2023.101558). In contrast, patients in India, Japan and Singapore have access to nearly all the cancer therapies and testing services at modest or no personal cost (Supplementary Tables S10-S12, available at https://doi.org/10.1016/j.esmoop.2023.101558). For example, in Singapore, testing is approved but not reimbursed and most cancer treatments are approved. Patients can pay out of their national savings scheme and basic health insurance plan for those agents that are approved (i.e. nearly all the drugs discussed in the main text above). There is also a complex insurance system for people who can afford it, and a means tested 'safety net' for those that cannot (Supplementary Table S12, available at https://doi.org/10.1016/j.esmoop.2023.101558). In Korea, nearly all tests and treatments are approved, but although the testing is reimbursed, the reimbursement of treatment is limited beyond first line (Supplementary Table S13, available at https://doi.org/10.1016/j.esmoop.2023.101558). In the case of Taiwan, there are limited approvals for both testing and therapy, with EGFR inhibitors and bevacizumab approved in first and third line, and first line only, respectively (Supplementary Table S14, available at https://doi.org/10.1016/j.esmoop.2023.101558). In China, most drugs and a number of targeted agents are available for the treatment of patients with mCRC, although several targeted agents as well as several genetic tests are not reimbursed (Supplementary Table S15, available at https://doi.org/10.1016/j.esmoop.2023.101558).

The differences between the countries reflect the way the different countries manage their health care systems and the money allocated from the individual governments to cancer care. Significantly, the health care systems of the more affluent countries offer a higher proportion of their populations access to all levels of cancer care due not only to

them having the highest rates of drug approvals and/or better public reimbursement policies, but also due to a higher percentage of their populations being able to purchase or obtain through their employment, private medical cover.

The individual statements, from the experts of each country, describing the availability and access to optimal diagnostic and molecular testing and the latest drug therapies for their individual countries, are described in the paragraphs below together with some of the details of their reimbursement policies.

China. In China, the drugs available for the treatment of patients with mCRC include the following, namely the chemotherapy drugs 5-FU, oxaliplatin, irinotecan, capecitabine and trifluridine—tipiracil, and the targeted agents cetuximab (for patients with *RAS* wt mCRC), bevacizumab, regorafenib and fruquintinib, and are reimbursed by medical insurance (Supplementary Table S15, available at https://doi.org/10.1016/j.esmoop.2023.101558). Pembrolizumab is also available for those patients with MSI-H mCRC but is not reimbursed. To date, the agents aflibercept, panitumumab, ramucirumab, encorafenib, adagrasib, sotorasib, lapatinib, tucatinib, trastuzumab deruxtecan and larotrectinib are still not available to Chinese patients.

Patients with mCRC can undergo recommended genetic testing, including for their *RAS*, *BRAF*, *HER2*, MSI status and for *NTRK* fusions. Currently, however, medical insurance in China only covers PCR testing for *RAS* (*KRAS/NRAS*) and *BRAF* alterations, and MSI testing. Medical insurance also covers immunohistochemistry (IHC) and fluorescence *in situ* hybridisation (FISH) detection of HER2 alterations, and IHC detection of MMR. Next generation sequencing (NGS) testing is not reimbursed by medical insurance. There are different policies in terms of reimbursement across the different provinces depending on province-based approvals.

Indonesia. In Indonesia the universal health care system (UHC) covers most of the health services. Although almost 80% of Indonesians are covered by the UHC, however, amongst them are individuals who also have their own private medical insurance or whose health care is covered by their employer.

The use of 5-FU-based chemotherapy (including oxaliplatin or irinotecan regimens) as first-line or second-line therapy is reimbursed, whilst targeted therapies and checkpoint inhibitors are not. Biomarker testing is available but not all tests are reimbursed. New technology-based tests (i.e. NGS) are not reimbursed. Also, after a Health Technology Assessment (HTA), bevacizumab and cetuximab for the treatment of mCRC have been excluded from the UHC scheme.

In terms of availability, in Indonesia new drugs/agents firstly have to receive approval from the Indonesian Food and Drug Authority (FDA). Then after 2 years an application can be made for the drug to be included in the national formulary which is a list of medications that are eligible to be given to patients under the UHC scheme. Due to the high burden of health care costs, however, especially for cancer treatment, it can sometimes take years, multiple scientific evaluations and cost effectiveness analyses/HTA, for a new drug to be listed under the national formulary for UHC. Thus, most of the drugs are not available or reimbursed for patients with CRC. Drugs are approved for very specific indications.

India. Most of the drugs (chemotherapy and biologicals) for the treatment of mCRC discussed in the ESMO guidelines[14] and Section A above are available in India (Supplementary Table S10, available at https://doi.org/10.1016/j.esmoop.2023.101558). Chemotherapy drugs and some of the biologicals are available in the government hospitals with cancer services and hence accessible to most patients at modest or no cost. India has a graded payment/insurance scheme based on patient income, decided by the government. Also, the wide availability of cheaper and good quality generics and biosimilars have improved patient access to better treatment. Drugs not covered by the government centres are covered by private insurance or by the patient as an out-of-pocket payment. The government health scheme covers about 30%-35% of the population, with the remainder taken care of by the private sector.

Most tests including NGS are available but are expensive. Limited PCR panels are widely available. Some of the tests are reimbursed by insurance providers, whereas some drug companies offer coupons to subsidise certain tests. Many centres conduct investigator-initiated studies to generate Indian patient data including on biomarkers, facilitating increased patient access to newer therapeutic strategies.

Japan. In Japan, all the drugs recommended in the ESMO Clinical Practice Guideline,[14] except for trastuzumab plus lapatinib and trastuzumab deruxtecan are approved and reimbursed (Supplementary Table S11, available at https://doi.org/10.1016/j.esmoop.2023.101558). In addition, the triplet combination of cetuximab plus encorafenib plus binimetinib in second or later line,[19,63] and trastuzumab plus pertuzumab in third or later line,[81] are approved and reimbursed.

All the recommended assays for biomarker analysis (except primary NGS), are approved and reimbursed. Also, repeated plasma-based digital PCR *RAS* testing for rechallenge of anti-EGFR therapies and NGS for comprehensive genome profiling after standard therapies are also both approved and reimbursed. Patients pay 0%-30% of the total cost for diagnostic/molecular testing and treatment, depending on their age and income.

Korea. All drugs and assays discussed above in Section A of this manuscript are available in Korea, except for ramucirumab and trastuzumab deruxtecan, as indicated in Supplementary Table S13, available at https://doi.org/10.1016/j.esmoop.2023.101558. Some biological agents or ICIs are also available beyond second line for patients with mCRC, but their cost is not reimbursed yet.

Malaysia. In Malaysia there are two types of health care system. The government provides universal health care

under the Ministry of Health (MOH) for all Malaysians for a very low fee. Alternatively there is private health care, which is not affiliated with MOH, for those who wish to and are able to pay for it.

Targeted drugs are very limited and are often not available widely under the MOH due to cost issues and are therefore generally not reimbursable. Malaysia does not practice a partly funded government health insurance policy for individual citizens. Common systemic chemotherapy regimens are covered but not the newer targeted therapies. Patients therefore often pay privately, often out of their own pocket or using some form of insurance (Supplementary Table S7, available at https://doi.org/10.1016/j.esmoop.2023.101558). Thus, in the private sector in Malaysia, targeted drugs are more readily available as the patients pay using their own money or private insurance.

The MOH tries to negotiate with the pharmaceutical companies, to lower their prices, while at the same time considering generic options whenever possible. Health Intervention Technology, a division in the MOH, often discusses cost—benefit ratios when coming to a decision to include certain drugs for use by the MOH.

The Philippines. Most of the drugs enumerated (Supplementary Tables S5 and S8, available at https://doi.org/10.1016/j.esmoop.2023.101558) are available in the Philippines, although not reimbursed, resulting in 100% out-of-pocket patient payments. Most laboratory tests and diagnostics are available in the big cities like Manila and in big treatment centres, thus, 'availability for all patients' is an issue. Some agents can be obtained for compassionate use from Hong Kong or Singapore. The Philippines comprises >7000 islands with a range of different procurement policies.

Singapore. In Singapore, ~90% of Health Sciences Authority-approved cancer treatments are on the Cancer Drug List (CDL), a list of clinically proven and cost-effective cancer treatments. Only indication-specific treatments in the CDL can be claimed under MediSave (MSV), MediShield Life (MSHL) and Integrated Shield Plans (IPs). MSV is a national medical savings scheme that mandates individuals to set aside part of their income to pay for their hospitalisation and outpatient expenses including cancer drugs listed on the CDL. MediShield Life is a basic health insurance plan which helps to pay for large hospital bills and outpatient treatments including selected cancer drugs. IPs include MSHL and private insurance plans that provide additional cover for cancer diagnostics and drugs. Patients receiving government-subsidised care in public health care institutions utilising drugs which are listed under the Standard Drug List and/or covered under the Medication Assistance Fund may receive an up to 75% subsidy in drug costs (based on their monthly per capita household income). Those in need of financial assistance who fulfil the means testing requirements are eligible for government financial subsidies such as Medifund. In Singapore, molecular assays (e.g. IHC, PCR and NGS) are not subsidised or reimbursed (Supplementary Table S12, available at https://doi.org/10.1016/j.esmoop.2023.101558). Indication-specific drugs that are not on the CDL such as lapatinib, pertuzumab and trastuzumab deruxtecan for CRC treatment are not subsidised or reimbursed.

Taiwan. All drugs and tests are available in Taiwan but not always covered by public insurance. The coverage of National Health Insurance in Taiwan is basically 'ALL or NONE' and the financial burden is huge and expected to increase further in the era of precision medicine and immuno-oncology. The availability of other medications for the same indication and future budget burden are the most important considerations, as well as the scientific results of pivotal trials, for decisions on reimbursement. This explains the reasons for the relatively limited coverage of expensive biologics (a maximum of 36 weeks reimbursement for bevacizumab), some of the new technology-based tests (i.e. NGS) and new treatments (e.g. ICIs in MSI-H mCRC) on the reimbursement list (Supplementary Table S14, available at https://doi.org/10.1016/j.esmoop.2023.101558). Also, in the case of patients receiving triplet therapy, only two agents are reimbursed with the cost of the third agent having to be paid for.

Thailand. In Thailand's health care system, there are three main reimbursement schemes including the Universal Coverage (UC) scheme, the Social Security Scheme (SSS) and the Civil Servant Medical Benefit Scheme (CSMBS). The majority of Thai people were covered by the UC and the SSS. All government employees and their dependents are covered by the CSMBS.

For the UC and SSS, the use of oxaliplatin- and irinotecan-based regimens as first-line or second-line therapy are reimbursable. Targeted therapies, ICIs and biomarker testing are not reimbursable.

For those under the CSMBS, in addition to chemotherapy, they are able to access targeted therapy and companion biomarker testing using a pre-authorised system. Six months of bevacizumab therapy is eligible for reimbursement for second-line therapy. Panitumumab is the only anti-EGFR agent that is reimbursed for patients with *RAS* wt advanced CRC, with two indications including first-line therapy with doublet chemotherapy only for patients with potentially resectable advanced CRC, and third-line therapy in combination with single-agent irinotecan. Regorafenib is also reimbursable for patients with chemotherapy-refractory disease (Supplementary Table S9, available at https://doi.org/10.1016/j.esmoop.2023.101558). Otherwise the medical expenses are not reimbursed.

The ESMO-MCBSs for the different systemic therapy options and new therapy combinations for the treatment of patients with mCRC are to be found at https://www.esmo.org/guidelines/esmo-mcbs/esmo-mcbs-scorecards?mcbs_score_cards_form%5BsearchText%5D=&mcbs_score_cards_form%5Btumour-sub-type%5D=Colon+and+R.

CONCLUSIONS

The results of the voting by the Asian experts both before and after the hybrid virtual/face-to-face working meeting

showed >80% concordance with the ESMO recommendations for the treatment of patients with mCRC[14] (Supplementary Table S2, available at https://doi.org/10.1016/j.esmoop.2023.101558). Following the virtual 'face-to-face' discussions, revisions were made to the wording of 'recommendations 1k, 1l (new recommendation), 3e, 3h, 3n, 4k, 4m, 4r, 4s, 4z, 4aa, 4k (new recommendation) and 5a (Table 1) and resulted in a 100% consensus being achieved in terms of acceptability for all the recommendations listed in Table 1, which constitute the consensus clinical practice guidelines for the treatment of patients with mCRC in Asia. The variations in the availability for the patients of the testing, drugs and therefore treatment possibilities, between the different countries, reflect the differences in the organisation of their health care systems and their reimbursement strategies and will have a significant impact on the implementation of the scientific recommendations. Thus, policy initiatives are advised in order to improve patient access to state-of-the-art cancer care, adapted for the heterogeneous socioeconomic situations in the different Asian countries.

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